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HEBERDEN ORATION*

A BROADER SPECTRUM OF SJØGREN'S SYNDROME AND ITS PATHOGENETIC IMPLICATIONS

BY

JOSEPH J. BUNIM

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland

Your invitation to deliver the 1960 Heberden Oration is a great honour which I cherish especially because of the profound respect my colleagues of the American Rheumatism Association and I have for the major contributions that the members of the Heberden Society have made toward a better understanding of the rheumatic diseases. The nature of the studies I wish to report in this lecture conforms rather obediently to the counsel given by the eminent biochemist, Professor A. Neuberger (1960), who terminated the preceding Heberden Oration "by expressing the belief that a study . . . particularly of the immunological reactions observed, may be more helpful to an understanding of connective tissue diseases than elucidation of collagen metabolism, important and interesting enough though this is to the biochemist and general biologist".

History

The history of the synthesis of Sjögren's syndrome is quite interesting. Filamentary keratitis, one of the components of the syndrome, was first described by Leber (1882). However, the association of filamentary keratitis with disease of the lacrimal gland and deficiency of tears was not recognized until much later by Stock (1925). At a meeting of the Clinical Society of London, Hadden of St. Thomas's Hospital reported a case of "dry mouth" or suppression of the salivary and buccal secretions" (Hadden, 1888). The patient was a widow of 65, who had xerostomia, and in addition deficiency of lacrimal secretions. "The woman told me", wrote Hadden, "that she had occasion

to cry but no tears would come . . . Nothing unusual could be detected by sight and by palpation in the parotid and submaxillary regions. There was no local affection of the lacrimal apparatus." At the same meeting another case of "dry mouth" was reported by Sir Jonathan Hutchinson. The first report of the association of filamentary keratitis and joint disease appeared in the following year; Fischer (1889) noted a case of combined "arthritis deformans" and keratitis filiformis. The significance of this association was emphasized by a paper read before the Ophthalmological Society of the United Kingdom by Mulock Houwer of Amsterdam (Houwer, 1927). This report included ten patients with "keratitis filamentosa" of whom six had arthritis. Houwer wrote, "It was difficult, however, to get more facts regarding the nature of the arthritis as most patients did not like to submit to a clinical examination. We imagined that possibly we were dealing with cases of irregular gout. This possibility occurred to us on examining patient No. 9 (a woman of 60), where the x-ray examination of the hands revealed some changes suggesting gout." Houwer ended his paper with the following sentence: "As in England gout seems to be far more prevalent than in the Netherlands, I am very curious to learn whether any of you have come across similar cases." J. Gray Clegg of Manchester replied that he had indeed noted on several occasions "conjunctivitis associated with rheumatoid or arthritic conditions (which) occurred chiefly, if not invariably in women, one of whom had peliosis rheumatica, and there was no tear secretion (Clegg, 1927).

In 1933, Henrik Sjögren published his monograph on "A New Conception of Keratoconjunctivitis Sicca". With precision and thoroughness,

* Delivered on December 2, 1960, at the Wellcome Foundation, London.

he correctly described many of the clinical components of the syndrome which now bears his name, as well as the histopathological changes in the conjunctiva, cornea, lacrimal and salivary glands, and mucous glands of the laryngeal wall. Sjögren concluded that "the frequent coincidence of ocular changes and hypofunction of lacrimal glands with diminution of salivary secretion, arthritic changes, and other symptoms generally found, indicates that we have to deal here with a general disease". The original series (Sjögren, 1933) consisted of nineteen cases. By 1951, it had increased to eighty, of which 62 per cent. had polyarthritis (Sjögren, 1951). During the decade from 1947 to 1956, five papers were published by other authors (Table I) which presented the converse, namely, the occurrence of keratoconjunctivitis sicca (KCS) or some of its components in rheumatoid arthritis. Collectively 153 such cases were found among 1,213 of rheumatoid arthritis, a mean prevalence of 13 per cent.

TABLE I
OCCURRENCE OF KERATOCONJUNCTIVITIS IN
RHEUMATOID ARTHRITIS

Author	Year	Cases of Rheumatoid Arthritis	Cases of Keratoconjunctivitis	Percentage
Stenstrom	1947	435	46	11
Reader, Whyte, and Elmes	1951	62	20	32
Lackington, Charlin, and Gormaz	1951	50	17	34
Gaulhofer	1954	456	40	9
Thompson and Eadie ..	1956	210	30	14
Total		1,213	153	13

Some confusion has arisen about the terms Mikulicz's disease, Mikulicz's syndrome, and Sjögren's syndrome. In 1888, Mikulicz reported the first case of benign, symmetrical, painless enlargement of the lacrimal and salivary glands, but dryness of the eyes or mouth was not noted (these findings were published in 1892). The term Mikulicz's disease has been used to designate those cases in which enlargement of the glands was caused by diffuse infiltration of lymphoid tissue, as described by Mikulicz in his original paper. The broader term, Mikulicz's syndrome, has been used to include in addition enlargement of the salivary and lacrimal glands produced by leukaemia, malignant lymphoma, tuberculosis, sarcoidosis, and other diseases. The relationship between Mikulicz's disease and Sjögren's syndrome was clarified by Morgan and Castleman (1953) and Morgan (1954), who concluded that the pathological changes in the

salivary glands in both conditions were identical and that "the condition characterized by chronic enlargement of the salivary or lacrimal glands, which in the past has been called Mikulicz's disease, may be a less highly-developed variant of a larger symptom complex, Sjögren's syndrome".

In the literature on both Mikulicz's disease and Sjögren's syndrome, one finds repeated mention of the similarity between the pathological changes in the lacrimal and salivary glands in these disorders and those in the thyroid gland in Hashimoto's thyroiditis. The first to draw attention to this analogy, we might add, was Hashimoto himself, in his original paper of 1912. The more recent discovery by Roitt and Doniach (1958) and Witebsky, Rose, Terplan, Paine, and Egan (1957) of circulating antibodies to thyroglobulin and thyrotoxic thyroid tissue in patients with Hashimoto's disease led Jones (1958) to search for organ-specific antibodies in patients with Sjögren's syndrome. Using the agar-gel diffusion precipitin test, Jones found antibodies to extracts of human lacrimal and salivary glands in the sera of three of 44 patients with Sjögren's syndrome. Jones's report was the final stimulus that activated our clinical and laboratory investigations of Sjögren's syndrome. Some observations made in the course of these investigations have been previously reported (Bloch, Wohl, Ship, Oglesby, and Bunim, 1960; Bloch, Bunim, Wohl, and Zvaifler, 1960).

The National Institutes of Health Series

This study exemplifies the type of multidisciplinary clinical research for which the facilities and organization of the N.I.H. are especially well designed. In less than 2 years, we were fortunate enough to assemble forty cases of Sjögren's syndrome. Most of the patients were admitted to the Arthritis Branch of the National Institute of Arthritis and Metabolic Diseases and several to the Ophthalmology and Neurology Branches of the National Institute of Neurological Diseases and Blindness. My principal co-workers were Drs. Kurt Bloch, Martin Wohl, Richard Oglesby, and Irwin Ship. Their loyal and effective assistance made this study possible. I am especially indebted to Dr. Bloch whose resourcefulness contributed major strength to this project.

Clinical, Pathological, and Laboratory Components of Sjögren's Syndrome

The diagnosis of Sjögren's syndrome is generally based on a triad of keratoconjunctivitis sicca, xerostomia (with or without enlargement of the

salivary glands), and rheumatoid arthritis (Sjögren, 1933), but it may also be made when any two of these three features are present (Morgan, 1954). In some cases of Sjögren's syndrome, systemic lupus erythematosus (Morgan, 1954), scleroderma (Oblatt, Fehér, and Csiky, 1958), or polyarteritis nodosa (Ramage and Kinnear, 1956) may replace rheumatoid arthritis in Sjögren's complex. Observations made in the course of the present study make it likely that a fourth major component, the presence of rheumatoid factor, might be added to the diagnostic criteria.

The numerous case reports that have appeared since Sjögren's monograph was first published have added a number of components to the original syndrome. In Table II the list is brought up to date. We have added six items which are noteworthy because of their occurrence in cases of Sjögren's syndrome without rheumatoid arthritis; namely, rheumatoid factor, complement-fixing antibodies to tissue components, thyroglobulin antibodies, arteritis, focal myositis, and neuropathy. We have also added two diseases not previously associated with this syndrome, namely myopathy or polymyositis (four cases) and Hashimoto's thyroiditis (two cases).

TABLE II
COMPONENTS OF SJÖGREN'S SYNDROME

I. Manifestations of Exocrine Gland Disorder	
Keratoconjunctivitis sicca	Pharyngo-laryngo-rhinitis sicca
Xerostomia	Tracheo-bronchitis (atelectasis, pleuritis*)
Enlarged salivary and lacrimal glands	Vaginitis
Dental caries	Achlorhydria
II. Manifestations of Other Organ Involvement	
Rheumatoid arthritis	Neuropathy
Splenomegaly	Alopecia
Hepatomegaly	Blood
Raynaud's phenomenon	Eosinophilia
Purpura	Leucopenia
Arteritis	Thrombocytopenia
Focal myositis	
III. Protein Abnormalities	
Hyperglobulinaemia	Rheumatoid factor
Cephalin flocculation	Tissue antibodies
Thymol turbidity	Thyroglobulin antibodies

* Pleuritis may be secondary to, or independent of, pulmonary parenchymal lesions.

The series studied at the N.I.H. consisted of forty patients. All but one were women. The ages ranged from 16 to 75 years (mean 50). The diagnosis was based on symptoms of dryness of the eyes, nose, mouth, or throat, and on the objective evidence of keratoconjunctivitis sicca, xerostomia and rheu-

matoid arthritis. At least two of these three conditions were present in all cases.

Clinical Subgroups of Sjögren's Syndrome.—The cases in this series fall conveniently into five subgroups on the basis of combinations of components of the syndrome (Table III).

- Group A, Sjögren's syndrome associated with classical or definite rheumatoid arthritis (17 cases);
- Group B, Sjögren's syndrome associated with possible rheumatoid arthritis (2 cases);
- Group C, Sjögren's syndrome associated with scleroderma (2 cases);
- Group D, Sjögren's syndrome associated with myopathy (4 cases);
- Group E, keratoconjunctivitis and xerostomia not associated with any other disease (15 cases).

TABLE III
CLINICAL SUB-GROUPS OF SJÖGREN'S SYNDROME

Group			No. of Cases
A	Sjögren's Syndrome	With classical or definite rheumatoid arthritis	17
B		With possible rheumatoid arthritis	2
C		With scleroderma	2
D		With myopathy	4
E	Sicca complex alone		15

The mean age at the time of observation of Groups A and B was 47 years; Group C, 32 years; and Groups D and E, 54 years.

Salivary and Lacrimal Glands.—Table IV shows that all but three patients had keratoconjunctivitis sicca, 35 had symptoms of xerostomia, and twenty

TABLE IV
OCCURRENCE OF CERTAIN COMPONENTS OF SJÖGREN'S SYNDROME IN NATIONAL INSTITUTES OF HEALTH SERIES (40 cases)

Component	Number	Percentage
Keratoconjunctivitis sicca	37	93
Xerostomia	35	88
Parotid enlargement	20	50
Rheumatoid arthritis		
Classical or definite	17	48
Possible	2	
Splenomegaly	10	25
Hepatomegaly	8	20
Raynaud's phenomenon	7	18
Pleural thickening (x-ray)	7	18
Pulmonary infiltration (x-ray)	7	18
Eosinophilia (above 3 per cent.)	21	53
Leucopenia (below 4,000)	13	33
Thrombocytopenia (below 150,000)	3	8
Thymol turbidity test (positive)	21	53
Cephalin flocculation test (positive)	18	45

gave a history or presented signs of enlargement of the parotid gland. The clinical impression of keratoconjunctivitis sicca was supported by typical biomicroscopic changes in the cornea, staining of the bulbar conjunctiva and cornea with rose-bengal dye, and diminished tear flow as measured by the Schirmer technique. The presence of xerostomia was documented by salivary flow studies. Secretory sialography was carried out on 31 of the forty patients. The sialogram was normal in only one case; mild to moderate changes (mild punctate to punctate patterns) were observed in sixteen, severe alterations (globular configuration) in seven, and advanced changes (cavitary or destructive pattern) in seven.

The microscopic alterations in the salivary and lacrimal glands have been previously characterized by others. Typically these consist of dense intra-lobular infiltration of lymphocytes, atrophy of acinar tissue, and proliferation of duct-lining cells. The cellular multiplication in the ducts results in narrowing or obliteration of the ductal lumen and often in the formation of solid cell masses or "epi-myoeptithelial islands". The lobular architecture by and large remains intact.

Biopsy of the parotid or submaxillary gland in thirteen patients in our series revealed extensive accumulations of lymphocytes and plasma cells with reduction of acinar parenchyma in almost all cases, proliferation of duct epithelium in eleven cases, and more advanced changes with formation of epi-myoeptithelial islands in seven cases.*

A similar infiltrative process may occur in the mucous glands of the pharynx and larynx, and in the submucous glands of the oesophagus (Cardell and Gurling, 1954), trachea, and bronchi (Bucher and Reid, 1959).

Vasculitis.—This had been observed previously at autopsy in three cases of Sjögren's syndrome associated with rheumatoid arthritis. The vascular lesions were described as periarteritis nodosa (Cardell and Gurling, 1954), acute necrotizing arteritis (Haas, 1951), and arteritis (Bucher and Reid, 1959). Since arteritis is very likely an integral part of the systemic pathological changes in rheumatoid disease, its occurrence in the above three cases may have been a manifestation of rheumatoid disease. However, Ramage and Kinnear (1956) reported a case of Sjögren's syndrome not associated with rheumatoid arthritis in which polyarteritis nodosa was found at necropsy. In our series

arteritis was found in two cases of definite rheumatoid arthritis and in one of possible rheumatoid arthritis. Of special interest, however, was the presence of vasculitis in random skin and muscle biopsies of three cases of Sjögren's syndrome without rheumatoid arthritis and in the absence of corticosteroid therapy. This lesion was not observed in seventeen other patients in our series who were subjected to muscle biopsy.

Two of the patients with arteritis had peripheral neuropathy. Sensory and motor changes were evident in the lower extremities and sensory changes alone in the upper. The neuropathy was mild in one case and disabling in the other.

Skeletal Muscle Involvement.—Myopathy (called polymyositis by others) was the prominent clinical feature in four cases. Muscle weakness was severe in two and moderate in two others. The proximal muscle groups were affected almost exclusively in three cases, while in the fourth both proximal and distal weakness were present. Muscle tenderness was absent in all four cases. Sensory function remained intact except for slight impairment of vibration sense in the lower extremities in three cases. The diagnosis of myopathy was confirmed electromyographically and histologically by muscle biopsy in each case.

It is evident that Sjögren's syndrome may occur in association with full-blown myopathy or polymyositis and would thus seem to be similarly related to this entity as it is to rheumatoid arthritis, scleroderma, and other connective tissue diseases.

Muscle biopsies were also done in nineteen of 36 cases without clinical evidence of myopathy. Mild chronic focal myositis was present in eleven patients, severe myositis in one patient with scleroderma, and moderate myositis in one patient with sicca complex alone. In a second patient of the latter group, granulomatous myositis was observed.

Other Clinical and Laboratory Components.—Splenomegaly was present in ten cases, hepatomegaly in eight, Raynaud's phenomenon in seven, and x-ray evidence of pleural thickening in seven and of chronic, basilar, mottled, and streaky infiltration in seven (Table IV). Eosinophilia (above 3 per cent.) occurred in 21, leucopenia (below 4,000 per c.mm.) in thirteen, and thrombocytopenia (below 150,000 per c.mm.) in three. Five patients had concurrent splenomegaly and leucopenia. In two of these, rheumatoid arthritis (Felty's syndrome) was also present. The thymol turbidity and cephalin flocculation tests were abnormal in 21 and 18 cases, respectively. These changes probably reflect alterations in serum protein rather than liver disease.

* Other causes of salivary gland enlargement (such as leukaemia, lymphoma, sarcoidosis, tuberculosis, cirrhosis, malnutrition, and Waldenström's macroglobulinaemia) were ruled out.

It is noteworthy that in 21 of the forty cases, a history of drug sensitivity was elicited. Of eight patients with rheumatoid arthritis known to have received gold, six had developed toxic reactions.

Renal Function Studies.—The frequent occurrence in our series of low urinary specific gravity not associated with proteinuria or other urinary abnormalities prompted more extensive study of renal concentrating ability in ten patients. In four, the ability to concentrate urine was decidedly abnormal. After 18 hours' dehydration and the administration of the anti-diuretic hormone, vasopressin, the mean milliosmol values in the four patients ranged from 362 to 665; the normal being above 900. All four had severe dryness of the mouth and two had definite polydipsia and polyuria. Since these patients had xerostomia, excessive water drinking as seen in psychogenic polydipsia first occurred to us as an explanation for the conspicuous hyposthenuria. However, when prolonged dehydration for 11 or 12 days failed to produce an increased urinary osmolality, this explanation became less tenable. Creatinine clearance tests were moderately abnormal in three and borderline in the fourth patient, but did not indicate renal impairment of a degree that would account for this lack of concentrating ability. Alternatively, the low urinary specific gravity may be explained by some organic lesion in the renal medulla which may have impaired primarily the tubular concentrating mechanism. At any rate, we have been so far unable to assess the full significance of the relationship of hyposthenuria in Sjögren's syndrome. Bucher and Reid (1959) found at necropsy, in a case of Sjögren's syndrome, dense infiltration of plasma cells and lymphocytes between the tubules in the medullary region. In that case, however, glomerulitis was also present.

Serological Studies

Serum Proteins.—Results of serum protein determinations in each of the five clinical groups previously delineated and in fifty normal controls are summarized graphically in the Figure (overleaf). Bars represent average values and the ranges of individual concentrations are indicated by brackets. In all groups the average serum albumin concentration was reduced below 3.4 g. per cent. The average serum globulin was increased above 3.5 g. per cent. Elevation of globulin was due chiefly to increase in gamma globulin, particularly the gamma 2 fraction, which on analytical ultracentrifugation proved to be the 7S type. Hyperglobulinaemia was present in every patient with myopathy (Group D) and in most patients with the sicca complex alone (Group E).

Rheumatoid Factor.—The results of tests for the rheumatoid factor by the bentonite flocculation test (BFT) on whole serum and the sensitized sheep cell agglutination test (SSCAT) on the euglobulin fraction, are presented in Table V. The BFT was positive in titres of 1:64 or higher in all cases, and the SSCAT in 83 per cent. of cases. This discrepancy may be due in part to the difference in sensitivity of the two tests. In three cases with sicca complex alone, moderate or high BFT titres and negative SSCA tests were encountered. Of special interest is the presence of rheumatoid factor in every one of the nineteen patients in Groups D and E, none of whom had rheumatoid arthritis or other connective tissue disease.

Antinuclear Factor.—The presence of antinuclear factor was detected by the indirect immunofluorescent technique, using as substrate frozen sections of mouse liver tissue. The sera of patients

TABLE V
SEROLOGICAL REACTIONS IN FORTY CASES OF SJÖGREN'S SYNDROME

Group			Positive BFT	Positive SSCAT	Antinuclear Factor*	Positive Comple- ment Fixation Test (Liver)
A	Sjögren's Syndrome	With definite rheumatoid arthritis ..	17/17	14/17	9/15 (16)†	2/17
B		With possible rheumatoid arthritis ..	2/2	2/2	1/2	2/2
C		With scleroderma	2/2	2/2	2/2 (256)	0/2
D		With myopathy	4/4	4/4	2/2 (64)	2/3
E	Sicca complex alone		15/15	11/15	10/10 (64)	13/15
Total			40/40 (100%)	33/40 (83%)	24/31 (77%)	19/39 (49%)

* By immuno-fluorescent technique with intact nuclei.

† Figures in () are reciprocals of median titres.

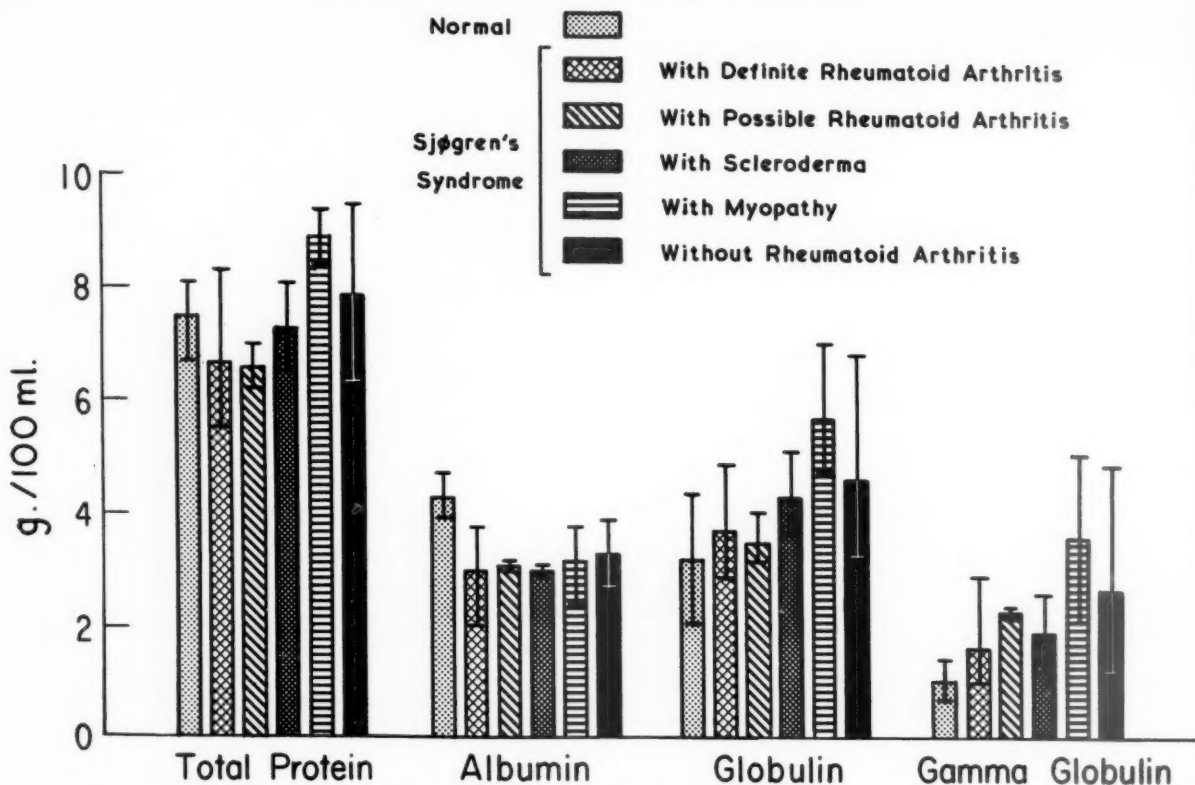


Figure.—Serum protein determinations (g./100 ml.) in normal subjects and five clinical groups of cases of Sjögren's syndrome.

tested were diluted serially to determine the titre for this factor; 77 per cent. of sera examined for this constituent were positive (Table V). Again it will be noted that the serum of every patient tested in Groups D and E contained this reactive substance and the median titre was 1 : 64. 60 per cent. of the patients with definite rheumatoid arthritis (Group A) exhibited positive reactions with a median titre of 1 : 16. In contrast, only 13 per cent. of 31 patients with rheumatoid arthritis without Sjögren's syndrome were positive. The specific nuclear constituent involved in these reactions is as yet undetermined. Repeated L.E. cell tests were performed in each of the forty cases of Sjögren's syndrome and were found to be positive in only three; and these three had severe rheumatoid arthritis.

Complement-Fixing Antibodies.—An attempt was made by complement-fixation techniques to demonstrate organ specific antibodies to salivary glands in sera of patients with Sjögren's syndrome. Experiments using a 10 per cent. suspension of human submaxillary gland as antigen demonstrated complement fixation, but it soon became apparent that

human liver, kidney, thyrotoxic and normal thyroid, and some striated muscle preparations provided antigens of approximately equal reactivity. Table V presents the results of complement-fixation reactions with the liver homogenate; 49 per cent. of 39 patients with Sjögren's syndrome fixed complement, the median titre being 1 : 360. Groups D and E again distinguish themselves from the others in the high incidence of complement-fixing antibodies; 83 per cent. in contrast to 12 per cent. in the cases of rheumatoid arthritis associated with Sjögren's syndrome. Moreover, the two patients in Group A had titres of only 1 : 40 and 1 : 120, whereas the median titre of the thirteen patients in Group E was 1 : 1,000. Differential ultracentrifugation of the tissue homogenates indicated that the active fraction in the complement-fixation test remains in the supernatant and does not sediment with the nuclei, mitochondria, or microsomes.

The reactions described appear to be analogous with those reported in the past 3 years from laboratories in several countries, including Australia, Great Britain, and the United States (Gajdusek, 1958; Mackay and Gajdusek, 1958; Asherson, 1959; Deicher, Holman, and Kunkel, 1960; Hackett,

Beech, and Forbes, 1960). These investigators found that sera of patients with certain chronic diseases fixed complement in the presence of human tissue homogenates (liver, kidney, lung, adrenal, and thyroid). Of the rheumatic diseases, systemic lupus erythematosus (SLE) was most prominent in their studies. It now appears that similar antibodies also occur in Sjögren's syndrome.

Our previous efforts to demonstrate precipitating antibodies to extracts of salivary glands in agar gel were unrewarding; however, current experiments using the patients' isolated gamma globulins and incubation at 37° C. have been more satisfactory. Precipitin lines were obtained with serum gamma globulins from several patients with Sjögren's syndrome and extracts from human liver, kidney, submaxillary gland, thyroid, and normal pooled gamma globulin. This reaction did not occur with controls.

Thyroid Studies

Because of the analogous histological alterations in Hashimoto's thyroiditis and Sjögren's syndrome, examination for clinical and laboratory evidence of thyroid disease or dysfunction was carried out in each case. In addition, sera were tested for thyroglobulin antibodies by haemagglutination tests using tanned erythrocytes coated with relatively pure thyroglobulin. Eleven of the forty patients had a positive tanned cell red cell agglutination test in titres ranging from 1 : 16 to 1 : 25,000. Of the eleven patients with thyroglobulin antibodies (Table VI), six had no clinical or laboratory evidence of thyroid disease, while five had either diffuse or nodular thyroid enlargement. Of these five, three were subjected to surgery; the tissue sections in two of them revealed diffuse changes consistent with Hashimoto's thyroiditis, and a thyroid nodule in the third case showed a few small foci of interstitial lymphocyte infiltration. One additional patient who had a negative thyroglobulin haemagglutination test had hypothyroidism. In this

series, then, five patients had both thyroid disease and thyroglobulin antibodies, but six of 34 (18 per cent.) had thyroglobulin antibodies without overt thyroid disease.* In this connexion it should be noted that Hackett, Beech, and Forbes (1960) reported that 30 per cent. of women over forty years of age admitted to the Royal Adelaide Hospital *without* clinically recognizable thyroid disease had positive thyroglobulin haemagglutination tests.

Sera of 129 relatives of eleven consecutive patients in our series and of 46 relatives of six control subjects were tested for thyroglobulin antibodies by the tanned red cell technique. The prevalence was 16 per cent. in the patients' relatives and 11 per cent. in relatives of controls. Of eleven patients' families studied, eight (72 per cent.) had two or more members with thyroglobulin antibodies, whereas only one of six (17 per cent.) control families exhibited this phenomenon. This difference would become statistically significant if sustained in a larger number of control and patient relatives. It is interesting that eleven of 21 relatives of patients had antibody titres of 1 : 1,024 or higher, whereas none of the relatives of controls had titres above 1 : 256. Extended family studies are currently in progress and will be reported subsequently.

Hall, Owen, and Smart (1960) searched for thyroid antibodies in the sera of 39 siblings of eleven probands with various types of thyroid disease (only one had Hashimoto's thyroiditis). Antibodies were found in 56 per cent. and half of these had no clinical evidence of thyroid disease. The authors concluded tentatively from these data that the predisposition to develop auto-antibodies to thyroid is inherited as a dominant characteristic.

The preliminary report by Hall and his associates requires confirmation. Determination of the significance of the difference in incidence of thyroglobulin antibodies in the relatives of probands with Sjögren's syndrome compared to that in the relatives of controls awaits completion of the family studies. It is conceivable that a genetic relationship exists between the occurrence of thyroglobulin antibodies and the development of Hashimoto's thyroiditis on the one hand and Sjögren's syndrome on the other. In this regard, it is of special interest that Hashimoto's thyroiditis has occurred in 5 per cent. of our cases of Sjögren's syndrome.

TABLE VI

OCCURRENCE OF THYROID ANTIBODIES AND THYROID DISEASE IN FORTY CASES OF SJÖGREN'S SYNDROME

Thyroglobulin Antibodies			Present	Absent
Number of Patients			11	29
Thyroid Disease	Nodular goitre	3 (1)	1*
	Diffuse enlargement	2 (1)	0
	None	6	28

() Hashimoto's thyroiditis.
* Hypothyroidism.

* The association of positive complement-fixation reaction employing antigens obtained from several tissues, including thyroid, with positive thyroglobulin haemagglutination reactions in some of the same sera may raise doubts as to the specificity of the latter. Indirect evidence suggests that these two phenomena are indeed independent of each other. Many sera which fixed complement in the presence of tissue homogenates did not react with thyroglobulin-coated tanned cells and some sera containing thyroglobulin antibodies either failed to fix complement in the presence of any tissue homogenate or did so only with thyrotoxic thyroid homogenate.

Discussion

It is quite apparent that Sjögren's syndrome, like systemic lupus erythematosus and rheumatoid arthritis, is a multisystemic disease. These conditions not only share certain clinical, pathological, biochemical, and serological characteristics, but also may indeed occur concurrently. Although the sicca syndrome is much more commonly associated with rheumatoid arthritis than with systemic lupus erythematosus, the high incidence of circulating antibodies to various tissue components in cases of Sjögren's syndrome without rheumatoid arthritis provides a noteworthy similarity to systemic lupus erythematosus. The analogy between Sjögren's syndrome and Hashimoto's thyroiditis is even more impressive.

Since efforts to discover the aetiology of rheumatoid arthritis and related diseases by employing older disciplines such as pathology, microbiology, and biochemistry have produced inconclusive results, the recent surge of interest in auto-immunity is understandable. While it is tempting to attribute pathogenic significance to circulating antibodies which act against tissue components *in vitro* (and the heuristic value of this concept is undeniable), one must examine critically the evidence thus far produced.

The criteria for an auto-immune disease as proposed by Witebsky and others (1957) consist of:

- (1) Demonstration of circulating or cell-bound antibodies;
- (2) Recognition of specific antigen against which this antibody is directed;
- (3) Production of antibody against the same antigen in experimental animals;
- (4) Appearance of pathological changes in the corresponding tissues of an actively sensitized experimental animal that are similar to those in human disease.

These criteria have not been fulfilled as yet in systemic lupus erythematosus, rheumatoid arthritis, or Sjögren's syndrome. Circulating antibodies in Sjögren's complex, with the exception of thyroglobulin antibodies, are neither organ nor species specific and a specific antigen has not yet been isolated or characterized chemically. Moreover, rabbits injected with homologous salivary gland homogenates and guinea-pigs injected with lacrimal glands homogenates in Freund's adjuvant failed to develop lesions in these organs (Bloch and McMaster, 1960).

It is still questionable whether the gamma globulins that participate in the serological reactions observed in these rheumatic diseases fulfil the criteria of classical antibodies. Are these so-called "anti-

bodies" produced in response to specific antigenic stimulation? Is it possible that the serological reactions may represent a relatively non-specific protein-protein interaction between a tissue component and a serum globulin that has been altered by a non-immunological process? Similar questions have arisen in well-studied test systems, such as the Wassermann reaction, and still await solution. Until further information is obtained concerning the significance of antibodies to tissue components, we must be conservative in our conclusions concerning their role in pathogenesis of disease.

However, the fact remains—all reservations and qualifications notwithstanding—that there is in Sjögren's syndrome and in certain connective tissue diseases, a high frequency of positive serological reactions, not only in the patients but also in an impressive percentage of their relatives. Could it be that the circulating factors with antibody-like characteristics do not necessarily act as the primary or direct pathogenic agent, but in some way alter the resistance of the host to subsequent attacks by as yet unidentified noxious agents? Such change in host resistance may be at the cellular level. It is conceivable that the presence of a circulating factor may merely reflect, and be of secondary importance to, the presence of cell-bound factors which thus far have eluded detection. Finally, may the source of trouble lie in the cells of origin of these so-called "antibodies" which, because of genetic factors, synthesize certain proteins (globulins) abnormally?

Summary

The studies reported here have broadened the spectrum of Sjögren's syndrome and have given additional support to Sjögren's original impression that the disease is systemic. The association of this syndrome with rheumatoid arthritis seems significant, although the basis for this linkage remains unexplained. Several features which rheumatoid arthritis alone shares with Sjögren's syndrome not associated with rheumatoid arthritis, such as vasculitis, neuropathy, and hyperglobulinaemia, are interesting. The high incidence of rheumatoid factor in this syndrome, even in the absence of rheumatoid arthritis, is intriguing. The unusual concurrence of Hashimoto's thyroiditis and Sjögren's syndrome (especially in view of a similar histopathological response in both conditions) and the frequent occurrence of thyroglobulin antibodies in the patients of this series require further investigation. The pathogenic implications of the high frequency of circulating antibodies to tissue components in this syndrome, as in certain other chronic diseases, are provocative but remain as yet obscure.

The interrelationship of the diverse diseases discussed in this lecture may be spurious, and I fear I may have compounded rather than reduced the confusion that currently envelops our concepts of the mechanism of these diseases. I confess that I have harboured the hope that what Lancelot Law Whyte said of theoretical science may apply to clinical science:

"The creative imagination rests on more than intense disinterested curiosity. The essential is the desire to understand multiplicity in terms of a single idea, to achieve insight by discovering a simple order within the apparent complexity. No one will undertake the effort of major discovery unless he is carried by an unquestioning, ardent belief, admitted or latent, that a simple underlying order exists or can be created."

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Un spectre plus large du syndrome de Sjögren et ses implications pathogénétiques

RÉSUMÉ

Les études présentées ici ont élargi le spectre du syndrome de Sjögren et renforcé la première impression de Sjögren qu'on y a à faire à une maladie générale. L'association de ce syndrome à l'arthrite rhumatoïdale semble significative, bien que la base de cette association demeure inexplicable. De différents traits communs de l'arthrite rhumatoïdale pure et du syndrome de Sjögren pur (c'est à dire non associé à l'arthrite rhumatoïdale), tels que vasculite, névropathie et hyperglobulinémie, sont intéressants. Il est aussi intrigant de trouver si souvent dans ce syndrome le facteur rhumatisal, même en l'absence de l'arthrite rhumatoïdale. La suprenante coexistence de la thyroïdite de Hashimoto et du syndrome de Sjögren (surtout en vue d'une réponse histopathologique similaire dans les deux maladies) et l'existence fréquente des anticorps contre la thyroglobuline chez des malades dans cette série demande aussi des recherches ultérieures. Les implications pathogénétiques de la grande fréquence des anticorps circu-

lants contre les composants tissulaires dans ce syndrome, comme dans certaines autres maladies chroniques, sont provocatrices mais toujours bien obscures.

Un espectro más amplio del síndrome de Sjögren y sus implicaciones patogénicas

SUMARIO

Los estudios presentados aquí han ensanchado el campo del síndrome de Sjögren y han dado un soporte adicional a la idea original de Sjögren de que se trata de una enfermedad general. La asociación de este síndrome con la artritis reumatoide parece significativa, aunque la base de dicha asociación permanece inexplicada. Varias características que la artritis reuma-

toide pura comparte con el síndrome de Sjögren puro (no asociado con artritis reumatoide), tales como vasculitis, neuropatía y hiperglobulinemia, son interesantes. Es intrigante la alta frecuencia del factor reumatoide en este síndrome aún en ausencia de artritis reumatoide concomitante. La insólita concurrencia de la tiroiditis de Hashimoto y del síndrome de Sjögren (especialmente en vista a una respuesta histopatológica similar en ambas enfermedades) y la frecuente aparición de anticuerpos contra la tiroglobulina en enfermos de esta serie requiere posterior investigación. Las implicaciones patogénicas de la alta frecuencia de anticuerpos en circulación contra los componentes de los tejidos en este síndrome, en similitud con otras enfermedades crónicas, son provocativas pero todavía permanecen oscuras.

PREVALENCE OF RHEUMATOID ARTHRITIS

BY

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In 1956, a committee of the American Rheumatism Association was formed to investigate diagnostic criteria for rheumatoid arthritis. They recommended that the disease should be classified into three categories: definite, probable, and possible, the classification being based on a points system.

The eleven points used for this classification included symptoms, physical signs, radiographic appearances, and laboratory tests (Ropes, Bennett, Cobb, Jacox, and Jessar, 1956, 1957, 1959). Though possessing certain limitations, particularly in relation to population studies in which the results of histological and synovial fluid examination are seldom available, these criteria do offer certain theoretical advantages over a simple clinical grading for rheumatoid arthritis. It was felt, therefore, that the publication of data on the American Rheumatism Association criteria in population samples drawn from an urban and a rural area in England might be of value to research workers in this country who desired a standard for comparison with their own findings.

Methods of Survey

The data used in this paper are drawn from two surveys: one in Leigh, Lancashire, based on a 1 in 30 random sample of persons aged 15 and over (Lawrence and Bennett, 1960); the other in Wensleydale, in the North Riding of Yorkshire, based on an area sample, including half the town of Hawes and half the villages in the area with their surrounding farms. In the Leigh sample there were 751 males and 814 females, in the Wensleydale sample 485 males and 540 females. Thus there was a total of 1,236 males and 1,354 females in the combined sample of whom 1,060 and 1,174 respectively were actually examined. The age and sex distribution was similar in these two areas and the completion rate (proportion of available persons having x rays

or a blood test or both) was also alike (86 per cent. in Leigh and 87 per cent. in Wensleydale). The clinical, radiological, and serological examination was based on the same routine procedure in Wensleydale and in Leigh, all persons having x rays of the hands, feet, and cervical spine. All x rays of the cervical spine were read by at least two observers. The sheep cell agglutination test was carried out by the method of Ball (1950).

American Rheumatism Association Criteria.—In assessing the American Rheumatism Association criteria, the clinical and radiographic criteria and the sheep cell agglutination test were used. Of the x-ray findings, only changes present in the hands and feet were included in the assessment.

Prevalence in Mixed Urban-Rural Population

"Definite"* rheumatoid arthritis was encountered in five males and nineteen females, "probable" disease in 21 and 52, and "possible" in 73 and 132 (Table I, overleaf).

If those falling into the "probable" and "definite" categories are accepted as having rheumatoid arthritis, the minimal prevalence (expressed as a proportion of the total in the sample) is 2.1 per cent. in males and 5.2 per cent. in females. In assessing the minimal prevalence it was assumed that none of those who were not examined had rheumatoid arthritis. The mean prevalence (expressed as a proportion of the total examined) was 2.5 per cent. in males and 6.0 per cent. in females. The true value must lie somewhere between these figures, since those who refuse to co-operate are generally persons without rheumatic symptoms.

The prevalence of "probable" and "definite"

* "Classical" rheumatoid arthritis has been included in the "definite" group.

TABLE I
AMERICAN RHEUMATISM ASSOCIATION CRITERIA APPLIED TO THE COMBINED
LEIGH AND WENSLEYDALE POPULATIONS

Age (yrs)	Males								Females							
	Total Sample	No. Examined	Disease				Percentage Probable and Definite		Total Sample	No. Examined	Disease				Percentage Probable and Definite	
			None	Possible	Probable	Definite	Minimum	Mean			None	Possible	Probable	Definite	Minimum	Mean
15-24	211	174	171	2	1	0	0.5	0.6	201	178	174	4	0	0	0	0
25-34	194	178	171	5	1	1	1	1	192	176	171	5	0	0	0	0
35-44	220	185	172	11	2	0	0.9	1	247	214	185	25	3	1	2	2
45-54	270	235	204	23	7	1	3	3	254	227	186	32	7	2	4	4
55-64	165	143	122	14	6	1	4	5	214	179	125	28	18	8	12	15
65-74	112	97	81	13	1	2	3	3	167	139	88	28	17	6	14	16
75+	53	48	40	5	3	0	6	6	72	61	42	10	7	2	13	15
Not stated	11	—	—	—	—	—	—	—	7	—	—	—	—	—	—	—
Total	1,236	1,060	961	73	21	5	2.1	2.5	1,354	1,174	971	132	52	19	5.2	6.0
Erosive Arthritis + Positive S.C.A.T.	7	1	1	2	3				14	3	0	1	10			
Erosive Arthritis Only	80	68	9	2	1				81	58	11	9	3			
Positive S.C.A.T. Only	31	25	1	4	1				39	33	3	1	2			
Percentage with Positive S.C.A.T.	4	3	3	29	80				5	4	2	4	63			
Percentage with Erosive Arthritis	8	7	14	19	80				8	6	8	19	68			

disease rose with age in both sexes, reaching a maximum of 6 per cent. in males aged 75 and over and 16 per cent. in females aged 65 to 74 years. The disease appeared at a rather earlier age in males, no females having "probable" or "definite" disease before age 35.

The proportion of positive sheep cell agglutination tests in the combined Leigh and Wensleydale populations was 4 per cent. in males and 5 per cent. in females. The sheep cell titre distribution in the Leigh and Wensleydale populations is to be discussed in detail in a further communication (Ball and Lawrence, 1961).

A positive sheep cell agglutination test was found in four of the five males with "definite" disease and in twelve of the nineteen females. Thus in 67 per cent. of "definite" cases the test was positive. Of the 21 males with "probable" disease, six (29 per cent.) had a positive sheep cell agglutination test, but of the 52 females with "probable" disease only two (4 per cent.) had a positive test. Those with "possible" disease had no more positive tests than those with "no" disease.

Radiological evidence of erosive arthritis was encountered in four (80 per cent.) of the five males with "definite" disease and in thirteen (68 per cent.)

of the nineteen females. Evidence of erosive arthritis was seen in 19 per cent. of both males and females with "probable" disease, in 14 and 8 per cent. respectively of those with "possible" disease, and in 7 and 6 per cent. respectively of those with "no" disease. The American Rheumatism Association criteria were thus found to be correlated with both the x-ray changes and the sheep cell test in both sexes.

Of the 1,042 males who were x-rayed, 87 (8 per cent.) had radiological evidence of erosive arthritis, and of the 1,157 females also 8 per cent. (Table II, opposite).

The proportion was thus the same in males and females and confirms earlier findings in population samples (Kellgren and Lawrence, 1956; Miall, Ball, and Kellgren, 1958). As indicated by the American Rheumatism Association criteria, the prevalence increased with age. In the 15- to 24-year group none of the males and only 1 per cent. of the females showed definite changes. In males aged 75 and over, on the other hand, 34 per cent. were considered to have definite evidence of erosive arthritis and the proportion was similar in females. Radiological changes were encountered most commonly in the cervical spine, the grading at this site

PREVALENCE OF RHEUMATOID ARTHRITIS

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TABLE II

RADIOLOGICAL EROSION ARTHRITIS (ALL SITES) IN LEIGH AND WENSLEYDALE, BY AGE AND SEX
(GRADINGS BASED ON THE READINGS OF ONE OBSERVER)

Age (yrs)	Males							Females						
	Total X-rayed	Grade						Total X-rayed	Grade					
		0	1	2	3	4	Percentage 2 to 4		0	1	2	3	4	Percentage 2 to 4
15-24	165	133	32	0	0	0	—	172	140	30	2	0	0	1
25-34	177	143	32	1	1	0	1	173	147	24	2	0	0	1
35-44	184	123	55	6	0	0	4	214	150	62	1	0	1	0.9
45-54	234	126	91	16	0	1	7	226	139	75	11	1	0	5
55-64	141	72	50	17	1	1	14	178	90	65	17	4	2	13
65-74	94	25	42	21	6	0	30	137	32	70	26	8	1	30
75+	47	10	21	12	3	1	34	57	10	28	14	1	4	33
Total ..	1,042	632	323	73	11	3	8	1,157	708	354	73	14	8	8

TABLE III

RADIOLOGICAL EROSION ARTHRITIS OF THE CERVICAL SPINE IN LEIGH AND WENSLEYDALE, BY AGE AND SEX
(GRADINGS BASED ON THE READINGS OF TWO OR THREE OBSERVERS)

Age (yrs)	Males						Females					
	Total <i>X</i> -rayed	Grade					Total <i>X</i> -rayed	Grade				
		0	1	2	3 to 4	Percentage 2 to 4		0	1	2	3 to 4	Percentage 2 to 4
15-24	165	146	19	0	0	—	170	156	12	2	0	1
25-34	176	157	19	0	0	—	172	163	9	0	0	0
35-44	183	162	20	1	0	0·5	213	194	18	0	1	0·5
45-54	233	182	45	6	0	3	224	189	27	7	1	4
55-64	139	101	27	10	1	8	174	119	44	8	3	6
65-74	93	36	39	15	3	19	137	76	34	21	6	20
75+	47	19	15	9	4	28	57	21	24	12	0	21
Total	1,036	803	184	41	8	5	1,147	918	168	50	11	5

being made by the criteria of Sharp, Purser, and Lawrence (1958). An average of the readings of two to three observers was used for Table III (above). The prevalence of rheumatoid arthritis by these criteria was 5 per cent. in both sexes, rising to 28 per cent. in males and 21 per cent. in females aged 75 and over. In view of the high prevalence of cervical arthritis in those aged 65 and over, it

must be considered whether degenerative disease produces a similar picture in old persons. This will be dealt with in a later communication. Erosive arthritis of the hands or feet (Table IV) was encountered in only 3 per cent. of both males and females, and was not found at all below age 25 in males or age 35 in females. Severe changes in hands and feet were seen in two males and six females.

TABLE IV

RADIOLOGICAL EROSION ARTHRITIS OF THE HANDS AND FEET IN LEIGH AND WENSLEYDALE, BY AGE AND SEX
(GRADINGS BASED ON THE READINGS OF ONE OBSERVER)

Age (yrs)	Males							Females						
	Total X-rayed	Grade						Total X-rayed	Grade					
		0	1	2	3	4	Percentage 2 to 4		0	1	2	3	4	Percentage 2 to 4
15-24	165	160	5	0	0	0	—	172	163	9	0	0	0	—
25-34	177	169	7	0	1	0	0.6	174	168	6	0	0	0	—
35-44	184	173	9	2	0	0	1	214	200	13	0	0	1	0.5
45-54	234	190	35	8	0	1	4	226	201	24	1	0	0	0.4
55-64	141	120	14	5	1	1	5	178	149	21	4	2	2	4
65-74	94	64	22	6	2	0	9	137	76	46	14	1	0	11
75+	47	28	15	3	1	0	9	57	32	16	5	1	3	16
Total ..	1,042	904	107	24	5	2	3	1,158	989	135	24	4	6	3

Comparison of American Rheumatism Association Criteria with Other Classifications of Inflammatory Polyarthrititis

(1) **Manchester Gradings.**—During the surveys in Leigh and Wensleydale each respondent was graded for severity of inflammatory polyarthrititis on a 0-4 scale. The gradings for each age group and the prevalences of Grades 2 to 4 (minimal, moderate, and severe) are shown in Table V. Grade 2 to 4 arthritis by this Manchester grading was found slightly more often in both males and females than the categories "probable" and "definite" by the American Rheumatism Association criteria, but the difference in prevalence was very slight, amounting to only 0·3 per cent. in males and 0·2 per cent. in females. The main differences between the two methods of grading are found in the females, the younger females appearing to have more arthritis by the Manchester scale, and the older females more by the American Rheumatism Association criteria. In the 25- to 34-year age group, for example, there were four females with arthritis by the Manchester scale and none by the American Rheumatism Association criteria. Of the four females concerned, three had "possible" rheumatoid arthritis and the fourth had a history of stiffness and swelling of the fingers lasting only 3 days which did not qualify her for the "possible" grade. However, this stiffness in the fingers was later followed by persistent subjective stiffness of the knees. It would thus appear that certain mild forms of polyarthrititis in young females are not included in the "probable" or "definite" grades of the American Rheumatism Association criteria and may also fail to be included in the "possible" group. The four females mentioned above all had a negative sheep cell agglutination test and lacked radiological erosions.

Of the 23 "probables" or "definites" in the 65- to

74-year age group in females, only thirteen had Grade 2 to 4 rheumatoid arthritis by the Manchester standard. Of the remaining ten, six had been given a doubtful grading for rheumatoid arthritis at the time and the remaining four had been diagnosed as generalized osteo-arthritis or osteo-arthritis of the knees. Thus, in the older females, a proportion of those with osteo-arthritis fall into the "probable" and "definite" group.

A comparison of the American Rheumatism Association criteria with the clinical grading for rheumatoid arthritis in Leigh is shown diagrammatically in the Figure (opposite), comparison being made with the clinical grading in an earlier survey of rheumatic complaints made in Leigh in 1950 (Kellgren, Lawrence, and Aitken-Swan, 1953). The two clinical gradings are in general closer to one another than are the American Rheumatism Association criteria to either.

(2) **Miall's Criteria.**—Miall and others (1958) assessed the prevalence of rheumatoid arthritis in South Wales. The criteria used for rheumatoid arthritis were a history of painful swellings of the hands or feet, with x-ray evidence of erosive arthritis in the hands or feet or a positive sheep cell agglutination test. The prevalence in random samples of persons aged 15 or more in South Wales by these criteria was 1 per cent. in each sex. At age 65 and over the maximum of 4 per cent. was attained.

When these criteria were applied to the Leigh and Wensleydale population samples (Table VI, opposite), a prevalence of 1 per cent. was found in males and 2 per cent. in females. Thus, by these criteria, the prevalence is about one-third of that estimated by the American Rheumatism Association criteria or the Manchester diagnostic grading. In the older age groups, where objective criteria are found in a

TABLE V
MANCHESTER CLINICAL GRADINGS FOR INFLAMMATORY POLYARTHRITIS APPLIED TO THE COMBINED LEIGH AND WENSLEYDALE POPULATIONS

Age (yrs)	Males							Females						
	Total Examined	Grade						Total Examined	Grade					
		0	1	2	3	4	Percentage 2 to 4		0	1	2	3	4	Percentage 2 to 4
15-24	174	166	7	1	0	0	0·6	179	165	14	0	0	0	—
25-34	178	163	11	3	1	0	2	175	160	11	4	0	0	2
35-44	185	169	12	4	0	0	2	214	180	24	9	0	1	5
45-54	235	207	19	6	3	0	4	227	177	37	11	2	0	6
55-64	143	131	7	2	2	1	3	179	136	24	12	4	3	11
65-74	97	84	10	1	1	1	3	139	96	23	16	3	1	14
75+	48	38	6	2	2	0	8	61	42	11	3	3	2	13
Total	1,060	958	72	19	9	2	2·8	1,174	956	134	55	12	7	6·3

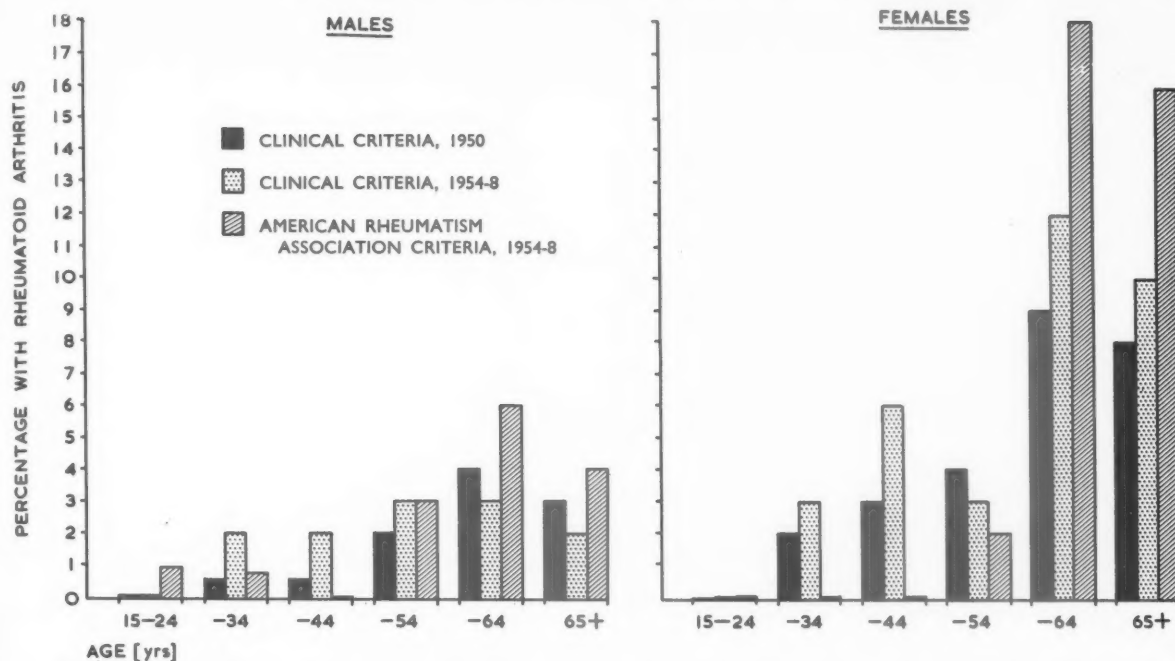


Figure.—Rheumatoid arthritis diagnosed clinically in the 1950 complaints survey and the 1954 to 1958 X-ray survey in Leigh, and by the American Rheumatism Association criteria in the latter; this diagram is based on unpublished material. The Wensleydale data have been excluded.

TABLE VI

MIALL'S CRITERIA APPLIED TO THE COMBINED LEIGH AND WENSLEYDALE POPULATIONS

Age (yrs)	Males			Females		
	Total Tested	Confirmed Rheumatoid Arthritis		Total Tested	Confirmed Rheumatoid Arthritis	
		No.	Per cent.		No.	Per cent.
15-24	172	0	—	180	0	—
25-34	172	1	0.6	167	0	—
35-44	181	0	—	209	1	0.5
45-54	231	3	1	215	2	1
55-64	138	2	1	168	7	4
65-74	95	3	3	130	6	5
75+	47	2	4	58	6	10
Total	1,036	11	1.1	1,123	22	2.0

high proportion of the population, the difference between Miall's criteria and the other two methods was less striking.

Discussion

Despite the many factors involved there is considerable agreement on prevalence between the American Rheumatism Association criteria and the Manchester clinical grading. Studies in seven different areas of Northern Europe have not produced evidence of any striking regional differences

in prevalence (Lawrence, Laine, and de Graaff, 1961), and it would therefore seem justifiable to apply the figures from Leigh and Wensleydale to the total adult population of Great Britain.

For this purpose the 1958 estimates of the population of England and Wales and the 1959 estimates for Scotland have been used, as these provide the most recent population data available. To avoid exaggerating the importance of this group of diseases, minimal prevalence figures for probable and definite

TABLE VII

ESTIMATED MINIMAL PREVALENCE OF RHEUMATOID ARTHRITIS IN GREAT BRITAIN, BY AGE AND SEX, 1959

Area	Age (yrs)	Total in Population		Rheumatoid Arthritis Probable and Definite	
		Males	Females	Males	Females
England and Wales	15-24	2,808,000	2,814,000	13,308	
	25-34	2,985,000	2,990,000	30,773	
	35-44	3,110,000	3,212,000	28,273	52,016
	45-54	3,161,000	3,284,000	93,659	116,362
	55-64	2,318,000	2,783,000	98,339	336,549
	65-74	1,396,000	2,028,000	37,393	279,305
	75+	676,000	1,211,000	38,262	151,375
	Total aged 15+	16,454,000	18,322,000	340,017 (2.1 per cent.)	935,607 (5.1 per cent.)
Scotland	15-24	348,600	366,700	1,652	
	25-34	343,700	351,100	3,543	
	35-44	328,000	347,500	2,982	5,627
	45-54	335,600	358,800	9,944	12,713
	55-64	250,000	304,100	10,606	36,775
	65-74	142,500	209,200	3,817	28,812
	75+	71,500	115,000	4,047	14,375
	Total aged 15+	1,819,900	2,052,400	36,591 (2.0 per cent.)	98,302 (4.8 per cent.)
Total in United Kingdom aged 15+		18,273,900	20,374,400	376,608 (2.1 per cent.)	1,033,909 (5.1 per cent.)

disease have been used (Table VII). By this estimate it can be said that at least 377,000 males and 1,034,000 females in Great Britain had "probable" or "definite" rheumatoid arthritis in 1959.

Summary

A random sample of 751 males and 814 females in the town of Leigh in Lancashire and an area sample of 485 males and 540 females in Wensleydale in Yorkshire have been investigated clinically, radiologically, and serologically to determine the prevalence of rheumatoid arthritis. The examination was completed in 86 per cent. of the Leigh sample and in 87 per cent. of the Wensleydale sample.

Using the American Rheumatism Association Criteria, the minimal prevalence of "definite" disease was 0.4 per cent. in males and 1.4 per cent. in females, and that of "probable" disease was 1.7 per cent. in males and 3.8 per cent. in females.

Radiological evidence of erosive arthritis was present in 8 per cent. of all those x-rayed, both males and females, but the disease was more severe in the females. Changes were most frequently encountered in the cervical spine. A positive sheep cell agglutination test was found in 4 per cent. of males and 5 per cent. of females.

It is estimated that, in Great Britain in 1959, approximately 377,000 males and 1,034,000 females had "probable" or "definite" rheumatoid arthritis.

All sheep-cell agglutination tests in these population samples were carried out by Dr. J. Ball of the Rheumatism Research Centre, Manchester University, to whom I am indebted for permission to use the results given in this paper.

I am also grateful to Prof. J. H. Kellgren, Dr. J. Sharp, and Mr. D. W. Purser for permission to use their x-ray readings on the cervical spine, and to Dr. J. Bremner, who carried out the original survey of Wensleydale as a research fellow of the University of Leeds.

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Fréquence de l'arthrite rhumatismale

RÉSUMÉ

Pour déterminer la fréquence de l'arthrite rhumatismale, on a examiné du point de vue physique, radiologique et sérologique deux échantillons de la population prise au hasard, l'un composé de 751 hommes et 814 femmes de la ville de Leigh en Lancashire et l'autre de 485 hommes et 540 femmes de Wensleydale en Yorkshire. L'examen a été complet en 86% de l'échantillon de Leigh et en 87% de celui en Wensleydale.

En appliquant les critères diagnostiques de la *American Rheumatism Association* on a trouvé que la fréquence minime de la maladie "définie" était de 0,4% parmi les hommes et de 1,4% parmi les femmes, et la fréquence de la maladie "probable" était de 1,7% parmi les hommes et de 3,8% parmi les femmes.

On a noté des signes radiologiques d'arthrite érosive chez 8% des hommes et des femmes radiographiés, mais la maladie était plus grave chez les femmes. Les lésions radiologiques les plus fréquentes se trouvaient dans la colonne cervicale. La réaction d'agglutination des globules de mouton était positive chez 4% des hommes et chez 5% des femmes.

On estime qu'au Royaume Uni, en 1959, à peu près 377.000 hommes et 1.034.000 femmes souffraient d'une arthrite rhumatismale "probable" ou "définie".

Incidencia de artritis reumatoide

SUMARIO

Para determinar la incidencia de la artritis reumatoide se estudiaron clínica, radiológica y serológicamente dos muestras de población tomadas al azar, una compuesta de 751 varones y 814 mujeres de la ciudad de Leigh en Lancashire y la otra de 485 varones y 540 mujeres de Wensleydale en Yorkshire. La investigación se llevó a cabo en su totalidad en el 86 por ciento de la muestra procedente de Leigh y en el 87 por ciento de la procedente de Wensleydale.

Empleando los criterios diagnósticos de la *American Rheumatism Association*, la incidencia mínima de enfermedad "definitiva" fue 0.4% entre varones y 1.4% entre mujeres, y la incidencia de enfermedad "probable" fue 1.7% entre varones y 3.8% entre mujeres.

Evidencia radiológica de artritis erosiva apareció en el 8% de los sujetos de ambos sexos examinados por este medio, pero la enfermedad era más grave entre las mujeres. Las alteraciones se detectaron con mayor frecuencia en la columna cervical. La reacción de aglutinación de los eritrocitos de carnero fue positiva en el 4% de los varones y el 5% de las mujeres.

Se estima que en el Reino Unido en 1959, aproximadamente 377.000 hombres y 1.034.000 mujeres padecían de "probable" o "definitiva" artritis reumatoide.

CHLOROQUINE DIPHOSPHATE IN RHEUMATOID ARTHRITIS*

A CONTROLLED TRIAL

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Page (1951), reporting on the value of treatment with the synthetic antimalarial mepacrine in lupus erythematosus, mentioned that one patient who had a polyarthritis of rheumatoid type showed simultaneous improvement of both the skin lesions and the arthritis. Since this report, the use of synthetic antimalarial compounds in the treatment of inflammatory polyarthritis has steadily increased; at the present time chloroquine and hydroxychloroquine are the drugs most commonly used.

Freedman (1956) reported a controlled trial of chloroquine in 66 patients with rheumatoid arthritis; over a period of 16 weeks the treated group, who received 200 mg. chloroquine sulphate daily, showed significantly greater clinical improvement than controls who were given dummy tablets; there was no significant change in haemoglobin concentration or erythrocyte sedimentation rate.

Cohen and Calkins (1958) described a double-blind controlled trial in 22 patients with rheumatoid arthritis of more than 1½ years' duration; half the patients were treated first with chloroquine phosphate in doses of 250-500 mg. daily for 10 weeks and then with dummy tablets for 8 weeks, and in the other half of the patients the order of treatments was reversed. During treatment with chloroquine there was a significantly greater improvement in morning stiffness and pain than when dummy tablets were given, but grip strength and erythrocyte sedimentation rate showed little change.

These reports indicated that treatment with chloroquine might have a favourable effect upon at least some of the clinical manifestations of rheumatoid arthritis, but, as the authors pointed out, the period of observation was not long enough

to assess the effectiveness of the treatment in relation to the natural history of the disease.

About twenty reports of the use of synthetic antimalarials in the treatment of rheumatoid arthritis have already been published. Few of these trials have been adequately controlled, and little would be gained by reviewing the reports in detail: in general terms, most authors have found that treatment with chloroquine or a related substance was of some value, while toxic effects were seldom serious, but were relatively frequent with doses in excess of 250 mg. daily of chloroquine diphosphate or its equivalent. Bagnall (1957) reported that 71 per cent. of a series of 108 patients with rheumatoid arthritis experienced remission or major improvement of symptoms during long-term treatment. Scherbel, Harrison, and Atdjian (1958) carried out a comparative trial of chloroquine and hydroxychloroquine in 106 patients, and concluded that there was little difference in the effectiveness of the two drugs; no control group was included, however, and the data do not establish the effectiveness of either treatment. Kersley and Palin (1959) reported 36 cases treated with alternating 3 months' courses of hydroxychloroquine sulphate, amodiaquine, and control tablets: as judged by clinical criteria, hydroxychloroquine produced worthwhile benefits in five of ten patients given doses of 800 mg. daily, but little effect in doses of 400 mg. daily.

The study reported here was undertaken with the aim of assessing the value of treatment with chloroquine in patients suffering from various types of inflammatory polyarthritis: it was thought desirable to determine whether the clinical improvement during short-term treatment, reported by others, would be apparent after continuous treatment for a year or longer and whether there would also be laboratory and radiological evidence of a beneficial effect. It was hoped, by the inclusion of adequate

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numbers of patients in the trial, that the results would indicate whether chloroquine treatment should be considered in the routine management of patients with inflammatory polyarthritis.

Material and Methods

The trial originally included patients suffering from polyarthritic syndromes other than rheumatoid arthritis, in separate controlled groups, but the numbers of patients in these other categories were too small for analysis. This report therefore deals only with the results of treatment with chloroquine in patients with an inflammatory polyarthritis of rheumatoid type.

Eligibility for Entry.—All patients with active rheumatoid arthritis admitted to the beds of the Rheumatism Unit in the Manchester Royal Infirmary or in the Devonshire Royal Hospital, Buxton, were eligible. The patients normally entered the trial during the second or third week after admission, when the results of the sheep cell agglutination test and other data were complete. A few patients who had by this time shown rapid improvement were not entered. The out-patients who were entered in the trial were those whose progress with conservative measures was not satisfactory; four had relapsed after in-patient treatment. The patients with rheumatoid arthritis who entered this trial were those for whom gold therapy would previously have been advised.

Diagnostic Criteria.—The criteria for entry into the trial were broadly similar to those used in the comparative trial of prednisolone with aspirin or other analgesics conducted by the Joint Committee of the Medical Research Council and Nuffield Foundation (Joint Committee Report, 1959), except that patients with disease of more than 24 months' duration were included as well as those with disease of 3 to 24 months' duration: patients of either sex with a rheumatoid type of arthritis affecting more than three joints, with bilateral involvement of hands or feet, ankles, or wrists were admitted. A positive result in the sheep cell agglutination test was not made a condition of entry but was used in the stratification of the patients into treatment groups.

Stratification and Allocation to Treatment.—All rheumatoid patients were stratified by sex and positive or negative result in the sheep cell agglutination test (SCAT). The patients showing a positive SCAT result were further stratified by duration of disease (3 to 24 months and over 24 months). As it was expected that there would be comparatively few patients with negative SCAT result eligible for the trial, these were not stratified by duration of disease.

The first patient in each of the six strata thus obtained was treated with tablets each containing 250 mg. chloroquine diphosphate: these tablets were referred to as Tablets "A".

The second patient in each stratum was treated with tablets each containing 2.5 mg. chloroquine diphosphate: these tablets were referred to as Tablets "B". The

alternation of treatments was continued so that consecutive patients in each stratum received different treatment.

Dosage of Chloroquine.—The tablets, which were sugar-coated, were identical in size, shape, and appearance. All in-patients were given one tablet twice daily while they were in hospital, and were instructed to take one tablet each evening when they returned home. Out-patients were treated with one tablet daily throughout. The patients were told that they were being given special tablets for rheumatism; their general practitioners were informed that this was a special chloroquine preparation and were asked to discontinue it in the event of serious toxic effects.

Other Treatment.—Chloroquine was given as an adjunct to whatever other treatment the patient would normally have received, except that gold was not used. The management of the patients followed a conservative regime of rest, splintage, and gradual mobilization, with modifications to suit the needs of individual patients. Analgesics were given as necessary: aspirin was most frequently used, but occasional patients were given other analgesics, such as tab. codein co. or phenylbutazone, if these appeared more effective. Some patients were treated with corticosteroids; the decision to do so was made independently of the fact that chloroquine was also being used, and was based on the currently accepted indications for steroid treatment (Empire Rheumatism Council, 1960).

Assessments.—During the course of the trial five different observers were indiscriminately concerned in making the assessments; four of the observers did not know which dose of chloroquine the tablets contained; the fifth (A.J.P.), who was concerned in the arrangements for the supply of the tablets and who did approximately a quarter of the follow-up assessments, was aware of their identity.

Assessments were entered on a form kept with the patients' notes, and were made on entry, at 1 month, at 6 months, and between 1 and 2 years after entry.

The methods of assessment were broadly similar to those used in the therapeutic trials conducted by the Joint Committee of the Medical Research Council and Nuffield Foundation (Joint Committee Reports, 1954). They included the following features:

- (1) At the initial assessment, the patient's score on the classification proposed by the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jassar, 1958).
- (2) At each assessment:
 - (a) Clinical assessment of disease activity, in four grades.
 - (b) General functional capacity, in five grades varying from normality (1) to complete crippling (5). (These grades are detailed under Table V.)
 - (c) Details of any symptoms or signs which might represent complications or side-effects of the treatment.

- (d) Haemoglobin concentration and erythrocyte sedimentation rate (Westergren).
 (e) Sheep cell agglutination test (Ball, 1950; Kellgren and Ball, 1959).
 (f) Strength of grip (mm. Hg). Average of three readings with each hand, with an initial bag pressure of 30 mm.
 (3) On entry and at follow-up after 12 to 24 months, x rays of hands and feet.

Number of Patients.—The total number of patients entering the trial was 134. The distribution of these patients between the two treatment groups by duration of disease, sex, and SCAT result is shown in Table I. 126 patients were classified as suffering from "definite" rheumatoid arthritis, as defined by the criteria proposed by the American Rheumatism Association (Ropes and others, 1958). The remaining eight patients, of whom five were in the treated and three in the control group, were classified as having "probable" rheumatoid arthritis; all these were females and seven had arthritis of

less than 24 months' duration and a negative sheep cell test.

Patients not Followed Up.—Twelve patients failed to complete the trial and are completely excluded from the analysis: these patients were not followed up and are shown in Table I as "Withdrawals with initial assessment only". The reasons for withdrawal are shown in Table IA and details are given in the Appendix.

Patients Followed Up but Excluded from Detailed Analysis.—In twenty of the 122 patients followed up, treatment with corticosteroids was given for more than 3 months, or, in the treated group, chloroquine was withdrawn because of toxicity (Table Ib). These twenty patients are shown in brackets in Table I; they are described in more detail below and are also included in the analysis of all patients followed up (Table VIII).

In six patients the period of follow-up was less than 1 year, but since the 6-months assessments were available and further observations had been made towards the

TABLE I
DISTRIBUTION OF PATIENTS AT ENTRY INTO TRIAL, BY SEX, DURATION, AND RESULT OF SHEEP CELL AGGLUTINATION TEST

Duration of Disease	Daily Dosage of Chloroquine Diphosphate (mg.)	Sheep Cell Agglutination Test Result					Total Followed Up	Withdrawals with Initial Assessment Only*	Total Entered
		Positive			Negative Females Only	Total in Trial			
		Males	Females	Total					
3 mths to 2 yrs ..	250-500	9 (1)	9 (3)	18 ² (4)	8 (1)	26 ¹ (5)	31	1	32
	2.5-5.0	6 (2)	9 (1)	15 ² (3)	6 (1)	21 ¹ (4)	25	3	28
Over 2 yrs	250-500	3 (2)	14 (4)	17 ³ (6)	6 (1)	23 (7)	30	6	36
	2.5-5.0	5 (0)	19 (4)	24 ³ (4)	8 (0)	32 (4)	36	2	38
Total	250-500	12 (3)	23 (7)	35 (10)	14 (2)	49 (12)	61 ⁴	7	68
	2.5-5.0	11 (2)	28 (5)	39 (7)	14 (1)	53 (8)	61 ⁴	5	66

* Table IA.

¹ Patients described in Tables III-V and IX-X.

² Patients described in Table VI.

³ Patients described in Table VII.

⁴ Patients described in Table VIII.

Figures in brackets represent twenty patients followed up though receiving steroids and also those in whom chloroquine treatment was stopped owing to toxicity (Table Ia).

TABLE IA
PATIENTS EXCLUDED FROM ANALYSIS

Reason for Exclusion	Treated	Control
Death early in trial ..	1	1
Refusal to attend ..	1	2
Patient untraceable ..	1	0
Chloroquine toxicity*	1	0
Wrong treatment ..	0	2
Changed diagnosis ..	1	0
Psychosis ..	1	0
Transfer for surgery ..	1	0
Total ..	7	5

* All other patients with symptoms possibly related to chloroquine treatment were followed up.

TABLE Ib
PATIENTS FOLLOWED UP THOUGH RECEIVING STEROIDS, AND THOSE IN WHOM TREATMENT WAS STOPPED

Treatment		Treated	Control
Treated with Steroids	Continued chloroquine ..	3	6
	Stopped chloroquine		
	Without having experienced toxicity ..	3	1
	Because of toxicity ..	2	1
Chloroquine toxicity, but not receiving steroids		4*	0
Total ..		12	8

* These four patients all had disease of more than 2 years' duration.

end of the first year these patients are included in the detailed analysis. One of these who died is described below.

Duration of Treatment.—Of the 102 patients used in the detailed analysis, who completed the trial according to plan and who were not treated with steroids, 93 (46 treated, 47 controls) received the prescribed treatment throughout the trial. In nine patients treatment was interrupted, but this was thought unlikely to have influenced the results of the trial; these patients are detailed below.

One control patient discontinued treatment after 8 months because of a rash, and one after 6 months because of dyspepsia.

Contrary to instructions, two control patients ceased taking the tablets when they were discharged from hospital since they were doubtful whether they were obtaining any benefit from them.

Three treated and two control patients temporarily discontinued treatment because of symptoms ascribed to toxicity, but resumed treatment when these symptoms had subsided.

Of the twenty patients shown in brackets in Table I and also in Table Ia, who were excluded from the detailed analysis, but were included in the final analysis of all 122 patients followed up (Table VIII), nine who had steroids (three treated, six controls) received the prescribed treatment throughout the trial. In eleven the tablets under trial were discontinued (in each case after less than 3 months) and in most instances the chloroquine was replaced by steroids.

Corticosteroid Treatment.—Of the 122 patients in the trial, eighteen received corticosteroid treatment, usually with prednisolone, at some period. Of these, two (one treated, one control) who had corticosteroid therapy for a few weeks only and were not receiving it at the times of assessment were included in the detailed analysis.

The remaining sixteen who received corticosteroids for more than 3 months were assessed at the usual times, but were excluded from the detailed analysis: these patients are among those shown in brackets in Table I; by chance, eight were in the treated and eight in the control group. Six of the sixteen were receiving steroids on entry and continued to receive them throughout the trial: six started steroid treatment within 2 months of entry: four had steroids for variable periods or started later in the trial. Seven of them (five treated, two controls) ceased taking chloroquine within a few weeks of entry, but the remainder continued to take both steroids and chloroquine. The dose of prednisolone ranged from 5 to 15 mg. daily; for those in the treated group the mean daily dose was 10.0 mg., and for the controls 8.8 mg.

The reason for embarking on steroid treatment was invariably that the patients were suffering from severe disease and had shown little or no improvement with conservative treatment. These patients formed too small a group for separate analysis but were included in

the analysis of all patients followed up (Table VIII), and it was found that inclusion or exclusion of corticosteroid-treated patients did not affect the conclusions.

Deaths.—Three patients died during the course of the trial. Two who died early in the trial are excluded altogether from the analysis, and are described in the Appendix. The third, who died after the 6-months assessment, is included in the analysis of clinical and laboratory data shown in Tables VII and VIII. This patient, a male aged 59 in the treated group, had severe nodular SCAT positive rheumatoid arthritis of 22 years' duration. He was treated as an in-patient for 3 weeks initially, but 3 months after discharge he stopped taking the tablets for 2 months, because he thought they made his legs swell; he had resumed treatment at the time of the 6 months' assessment. After attending for an interim interview 10 months after entry he developed a chest infection and died at home 3 weeks later: no autopsy was performed.

Toxicity.—Table II shows the number of times various symptoms were reported at different doses of chloroquine; 23 patients (thirteen treated, ten controls) reported symptoms which might have been due to chloroquine.

TABLE II
TOXICITY

Symptoms	Dose of Chloroquine Diphosphate (mg.)			
	500	250	5.0	2.5
Gastro-intestinal	4	3	1	4
Rashes	0	2	0	2
Dizziness	2	0	0	0
Visual disturbance	1	1	0	1
Headache	1	0	0	0
Insomnia	1	1	0	0
Other	0	1	1	1
Number of patients with symptoms at given dose levels	7	8	2	8
Chloroquine permanently withdrawn	5	2	0	3
Number treated	64	63	64	62
Total number of patients with symptoms	13		10	

Gastro-intestinal Symptoms.—These were reported by seven patients in the treated group, in five of whom chloroquine treatment was permanently discontinued on this account. These symptoms, which consisted of anorexia, nausea, vomiting, heartburn, epigastric pain, glossitis and dysphagia, and diarrhoea, were generally noticed after less than 2 weeks' treatment and subsided within a few days when it was withdrawn.

Five patients in the control group had gastro-intestinal symptoms, and in one of them treatment was permanently discontinued. These symptoms arose after more than 6 months' treatment and were generally slow to subside; they consisted of ulcer-type dyspepsia and various non-specific symptoms.

Visual Disturbances.—These were experienced by two patients in the treated group. One developed micropsia and dizziness after 2 weeks' treatment with 500 mg. daily. The other complained of gradually failing vision after 6 months' treatment with 250 mg. daily; he was found to have bilateral cataract, but slit-lamp examination showed the cornea to be clear; on entry to the trial he had had active scleritis which responded well to treatment with cortisone locally and prednisolone by mouth.

A woman in the control group complained of failing vision after a year's treatment with one tablet daily; she too was found to have incipient cataract when examined at another hospital, and no corneal abnormality was reported.

Rashes.—Two patients in the treated group had rashes. One developed a maculo-papular rash on the trunk after 2 weeks' treatment with 250 mg. daily; the rash disappeared a few weeks after chloroquine was stopped. The other developed an itching rash on the breast and trunk after 2 months' treatment with 250 mg. daily; the rash, which had the features of a neuro-dermatitis, did not improve when chloroquine was stopped for a few weeks, while the joint symptoms became worse; treatment was resumed and later the rash slowly cleared.

Two patients in the control group had rashes. One developed a rash almost certainly due to phenobarbitone sensitivity on the hands and forearms. The other developed a rash on the face after 7 months' treatment with one tablet daily; the rash disappeared when chloroquine was stopped but recurred when it was resumed.

Miscellaneous Symptoms.—Headache attributed to chloroquine was complained of by one patient in the treated group while taking 500 mg. daily.

Dizziness was experienced after 5 and 14 days' treatment respectively, by two patients in the treated group on 500 mg. daily; it subsided within a few days when treatment was withdrawn.

Insomnia was complained of by two patients in the treated group. In one who also developed glossitis and dysphagia chloroquine was withdrawn. The other noticed the symptom after 3 weeks' treatment with 250 mg. daily; mild sedation was effective and she was able to continue treatment.

Oedema was complained of by one treated and one control patient, but its relation to the treatment was very doubtful.

One patient in the control group complained of menorrhagia after 3 weeks' treatment with one tablet daily.

In seven patients in the treated group the use of chloroquine was abandoned because of toxicity: six of these had chloroquine for less than 2 weeks and the seventh for less than 6 weeks; no patient in this group developed severe toxic symptoms at a later date. Of the remaining six in the treated group who had symptoms which might have been due to chloroquine, three stopped the treatment temporarily and three continued it without interruption. Only one patient in the control group developed symptoms of any severity early in the trial: this was the woman who had menorrhagia, and it seems most unlikely that this was related in any way to her treatment; the remaining nine patients in the control group all developed symptoms after more than 6 months' treatment.

Symptoms which might have been related to the treatment were therefore observed in thirteen of the 68 patients originally entered in the treated group, a total incidence of 19.1 per cent.: ten out of 66 patients entered in the control group complained of symptoms attributed by themselves at least partly to the treatment, a total incidence of 15.2 per cent. On the other hand the real incidence of toxic effects may well be lower than these figures would suggest: three patients in the treated group and nine in the control group had symptoms which were doubtfully related to chloroquine treatment, and if these patients are excluded the incidence falls to 14.7 per cent. in the treated and 1.5 per cent. in the control group.

Comparability of Treatment Groups

Tables III to X show that the treatment groups were reasonably comparable on entry, and although there were minor differences in the various characteristics these did not approach conventional levels of significance. A difference between the groups in respect of one characteristic was to some extent balanced by a difference of opposite direction in another characteristic, and in general the differences tended to favour the control group.

Of the sixty patients with disease of 3 to 24 months' duration, only eighteen (30 per cent.) had symptoms of less than 1 year's duration, and of these early cases ten were in the treated and eight in the control group.

The mean ages of the patients in each treatment group varied between 45 and 49 years for those with a positive sheep cell agglutination test, both for those with recent and for those with long-standing disease. Of the patients with a negative sheep cell test, those with recent disease were slightly older (mean 52 years) and those with long-standing disease slightly younger (mean 43 years): the age distributions of the treated and control patients were similar.

Results

Table I shows that the trial included many patients with disease of more than 2 years' duration; a number of these had such severe joint destruction on entry that their capacity for improvement in function was limited and it was difficult to assess progression or improvement in the radiological changes. In order that the results of this trial might be compared with those of the prednisolone/analgesics trial conducted by the Joint Committee, a detailed analysis of patients with disease of less than 2 years' duration, irrespective of the results of the initial SCAT, will be considered first (Table III and Fig. 1, opposite; Tables IV and V, IX and X, overleaf).

TABLE III

AVERAGE GRADINGS AND MEASUREMENTS OF VARIOUS CHARACTERISTICS IN ALL PATIENTS
WITH DISEASE OF 3 TO 24 MONTHS' DURATION

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Disease Activity Grading	Functional Capacity Grading	Strength of Grip		Erythrocyte Sedimentation Rate (mm./hr)	Hb (g. per cent.)	S.C.A.T. (tubes above or below min. pos.)	X-ray Grading hands + feet 2
				mm. Hg	Per cent. of Higher Reading				
(a) Entry	250-500	1.81	2.85	170		42	12.4	+0.92	1.40
	2.5-5.0	1.90	2.80	164		34	12.7	+0.42	1.31
b) After 1 yr ..	250-500	0.83	1.83	228		23	12.7	-0.96	1.65
	2.5-5.0	1.54	2.26	186		46	12.8	+0.24	1.64
(b)-(a)	250-500	-0.98	-1.02	+58	+25.5	-19	+0.3	-1.88	+0.25
	2.5-5.0	-0.36	-0.54	+22	+5.8	+12	+0.1	-0.18	+0.33

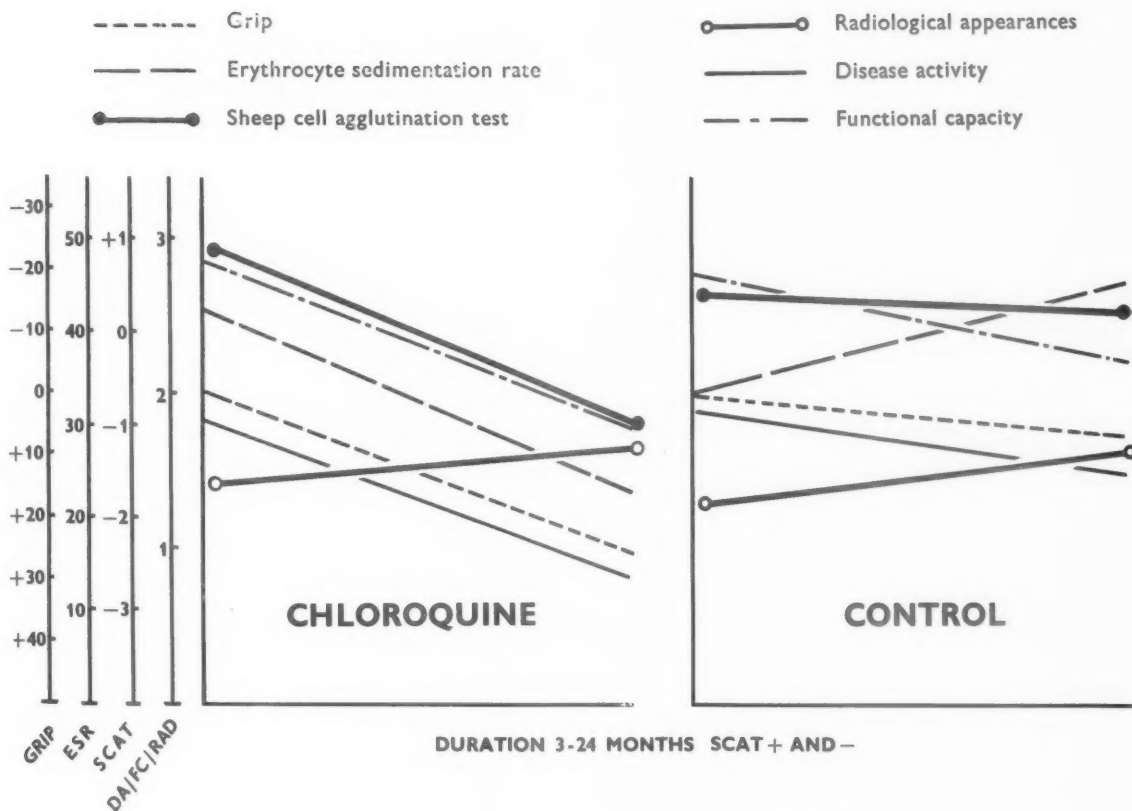


Fig. 1.—Diagrammatic representation of the data in Table III.

Tables IV and V show the numbers of patients in the two treatment groups with given grades of disease activity and functional capacity at entry and at follow-up. The two groups were reasonably well balanced in terms of these characteristics at

entry; on follow-up both groups showed improvement, but the group treated with the higher dose showed greater improvement in both characteristics the difference in disease activity being significant ($p < 0.02$); the difference in functional capacity

TABLE IV
NUMBER OF PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION WITH GIVEN GRADES OF DISEASE ACTIVITY

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Grade of Disease Activity				Total	Change in Grade (b)-(a)				
		0 to ½	1 to 1½	2 to 2½	3 to 3½		+1½ to +2	+½ to +1	±0 to -½	-1 to -1½	-2 to -2½
(a) Entry	250 to 500 2.5 to 5.0	5 1	5 6	9 11	7 3	26 21					
(b) After 1 yr ..	250 to 500 2.5 to 5.0	11 4	13 8	2 6	— 3	26 21	— 1	2 1	8 13	9 5	7 1

Grade: 0 = None 1 = Slight 2 = Moderate 3 = Severe.

TABLE V
NUMBER OF PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION WITH GIVEN GRADES OF FUNCTIONAL CAPACITY

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Grade of Functional Capacity					Total	Change in Grade (b)-(a)						
		1	2	3	4	5		+4	+3	+2	+1	±0	-1	-2
(a) Entry	250-500 2.5-5.0	2 3	7 2	11 12	5 4	1 —	26 21							
(b) After 1 yr ..	250-500 2.5-5.0	6 4	18 10	2 6	— —	— 1	26 21	— 1	— —	— —	— 1	10 8	7 7	8 2

Grade: 1 = Fully employed or employable in their normal work and able to undertake normal physical recreations for their type.
2 = Fully employed in their special work after vocational training, or doing light or part-time work in normal occupations. Limitation in the amount of physical recreation that can be taken. Housewives, all except the heaviest housework. In-patients, in hospital for investigation only.
3 = Patients not employed or employable. Very limited physical activity and little or no capacity for physical recreation. Housewives, light housework and/or limited shopping only. In-patients in hospital for treatment, but up and about in the ward.
4 = Confined to hospital, house, or wheelchair, but able to look after themselves in the essentials of life. In-patients in hospital for treatment, sitting up but not getting about.
5 = Confined to bed and unable to look after themselves. In-patients on complete bed rest.

is not formally significant. The changes in grip strength, erythrocyte sedimentation rate, and haemoglobin concentration are shown in Table III. The treated patients showed a significantly greater improvement in grip strength* ($p < 0.02$) and in erythrocyte sedimentation rate ($p < 0.001$); in the control group there was a slight improvement in grip strength, but the mean erythrocyte sedimentation rate was higher at follow-up. The changes in haemoglobin concentration are not significant, both groups showing a marginal improvement which was slightly greater in the treated group. The changes in the SCAT and the radiological changes are considered below.

* Improvement measured in per cent. of final, deterioration in per cent. of initial average reading.

Separate analyses were made of the two SCAT-positive sections of the sample—those with disease duration of 3 to 24 months and of more than 2 years—and of all cases followed up irrespective of duration of disease and SCAT result and including those treated with corticosteroids and those in whom chloroquine was withdrawn. The results are shown in Table VI and Fig. 2 (opposite), and in Tables VII and VIII, and Figs 3 and 4 (overleaf).
In practically every instance the changes recorded at follow-up were in the same direction as those observed in the complete group of patients with disease of short duration (Fig. 1). The differences between the changes in the two treatment groups in patients with disease of short duration and positive SCAT are even greater than when patients with negative SCAT are included, and they show, in spite

TABLE VI

AVERAGE GRADINGS AND MEASUREMENTS OF VARIOUS CHARACTERISTICS IN PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION AND POSITIVE REACTION TO THE SHEEP CELL AGGLUTINATION TEST

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Disease Activity Grading	Functional Capacity Grading	Strength of Grip		Erythrocyte Sedimentation Rate (mm./hr)	Hb (g. per cent.)	S.C.A.T. (tubes above or below min. pos.)	X-ray Grading hands+feet 2
				mm. Hg	Per cent. of Higher Reading				
(a) Entry ..	250-500	1.89	2.78	172		45	12.6	+2.61	1.41
	2.5-5.0	1.93	2.93	157		38	12.8	+2.00	1.58
(b) After 1 yr ..	250-500	0.89	1.78	236		21	12.6	+0.21	1.74
	2.5-5.0	1.67	2.37	173		50	13.0	+1.93	1.88
(b)-(a) ..	250-500	-1.00	-1.00	+64	+28.4	-24	±0.0	-2.39	+0.33
	2.5-5.0	-0.26	-0.56	+16	+4.1	+12	+0.2	-0.07	+0.30

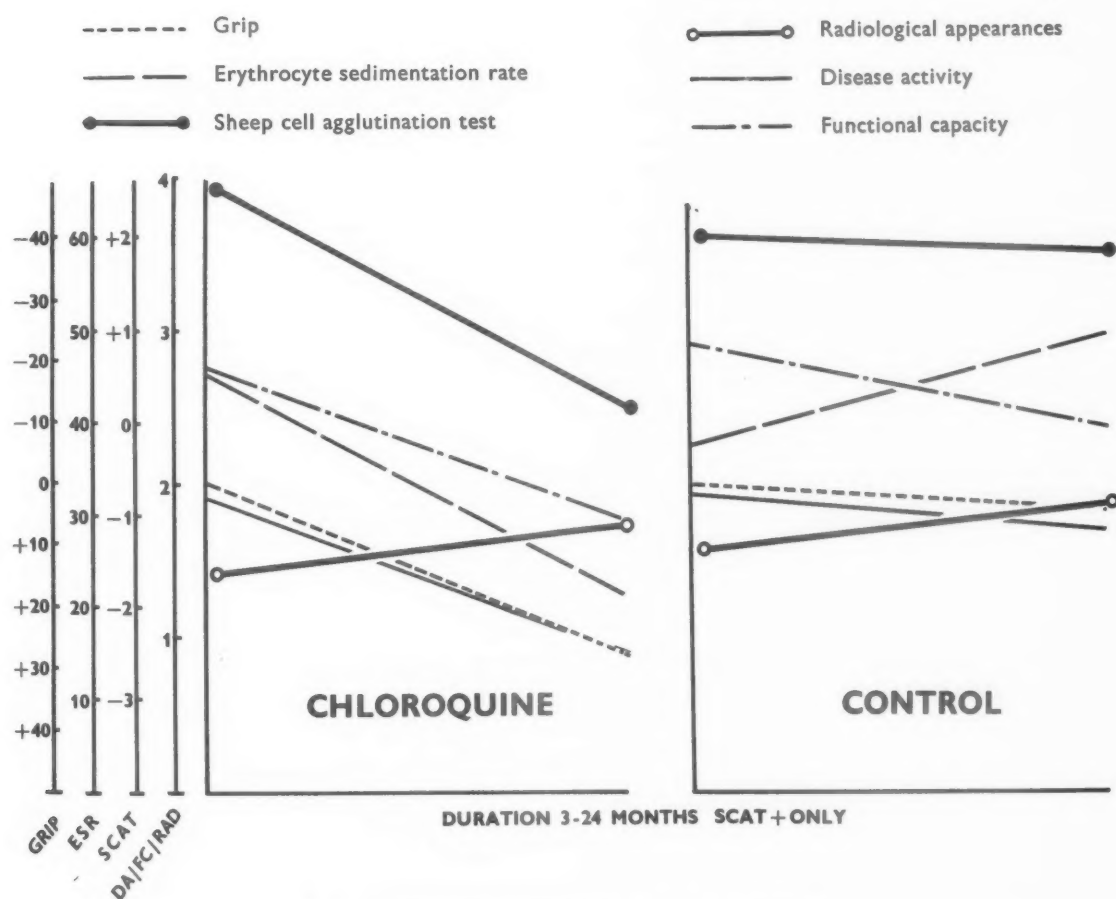


Fig. 2.—Diagrammatic representation of the data in Table VI.

of the small number of patients in this section, a significant advantage to the treated group in disease activity ($p < 0.05$), percentage increase in grip strength ($p < 0.02$), and erythrocyte sedimentation rate ($p < 0.001$). As might be expected,

the changes among the SCAT-positive patients with disease of long duration are less striking, and the differences between the changes in the two treatment groups reach formal significance only in functional capacity ($p < 0.01$).

TABLE VII

AVERAGE GRADINGS AND MEASUREMENTS OF VARIOUS CHARACTERISTICS IN PATIENTS WITH DISEASE OF MORE THAN 2 YEARS DURATION AND POSITIVE REACTION TO THE SHEEP CELL AGGLUTINATION TEST

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Disease Activity Grading	Functional Capacity Grading	Strength of Grip		Erythrocyte Sedimentation Rate (mm./hr)	Hb (g. per cent.)	S.C.A.T. (tubes above or below min. pos.)	X-ray Grading hands + feet 2
				mm. Hg	Per cent. of Higher Reading				
(a) Entry ..	250-500	1.62	3.21	130		41	12.2	+2.41	2.79
	2.5-5.0	1.98	2.90	106		41	12.0	+2.21	2.73
(b) After 1 yr ..	250-500	1.06	2.24	165		28	13.1	+1.12	2.79
	2.5-5.0	1.77	2.85	124		38	13.1	+1.33	2.89
(b)-(a) ..	250-500	-0.56	-0.97	+35	+22.3	-13	+0.9	-1.29	±0
	2.5-5.0	-0.21	-0.05	+18	+13.3	-3	+1.1	-0.88	+0.16

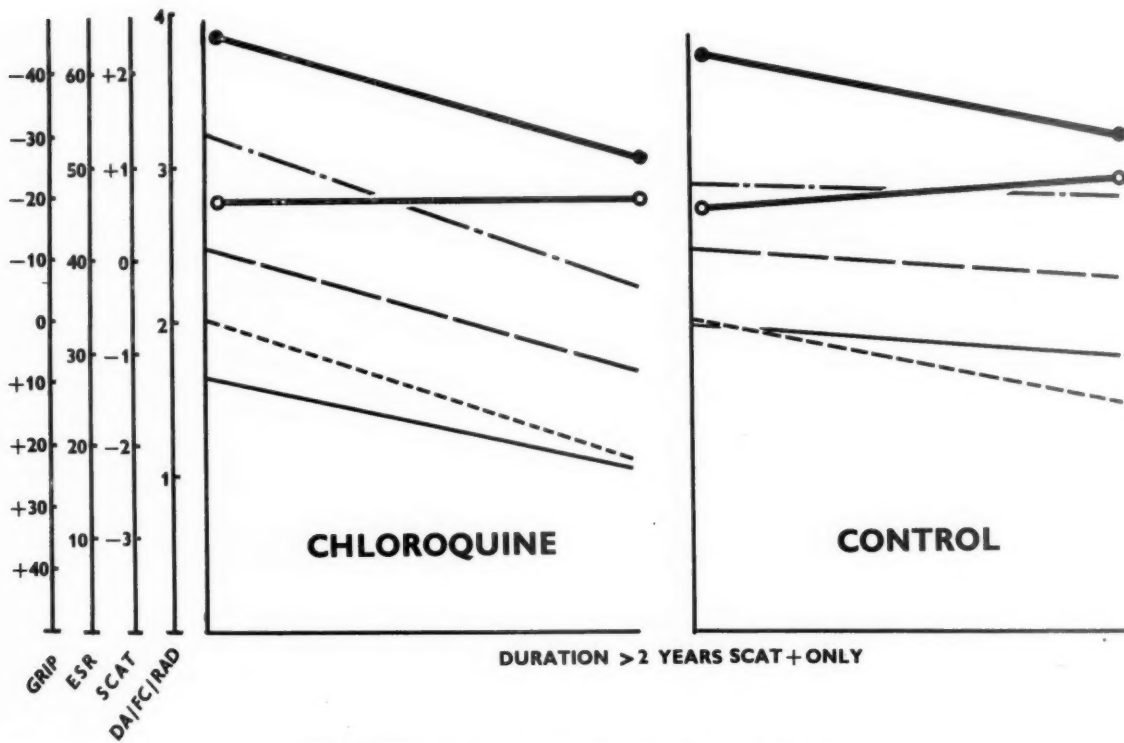


Fig. 3.—Diagrammatic representation of the data in Table VII.

When all the cases followed up are taken together (Fig. 4), the size of the changes lies between those for the short and long duration groups. In this large sample the differences in changes between treatment groups are all formally significant (disease activity $p < 0.01$; functional capacity $p < 0.05$; per cent. change in grip $p < 0.02$; erythrocyte sedimentation rate $p < 0.01$). Two reservations have to be made, however. The greater proportion

of long-duration cases in the control group introduces a bias in favour of the treated group, as also previously found by Duthie, Thompson, Weir, and Fletcher (1955); on the other hand, the inclusion in both treatment groups of patients who had corticosteroids and those in whom chloroquine was withdrawn acts in the opposite direction: it is probable that the effects of these opposing factors balance each other to some extent.

TABLE VIII

AVERAGE GRADINGS AND MEASUREMENTS OF VARIOUS CHARACTERISTICS IN ALL PATIENTS FOLLOWED UP

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Disease Activity Grading	Functional Capacity Grading	Strength of Grip		Erythrocyte Sedimentation Rate (mm./hr)	Hb (g. per cent.)	S.C.A.T. (tubes above or below min. pos.)	X-ray Grading hands + feet 2
				mm. Hg	Per cent. of Higher Reading				
(a) Entry ..	250-500	1.76	3.04	145		41	12.2	+1.11	2.06
	2.5-5.0	2.02	2.93	132		40	12.3	+0.87	2.07
(b) After 1 yr ..	250-500	1.02	2.13	187		30	12.9	-0.22	2.22
	2.5-5.0	1.70	2.52	150		41	12.8	+0.39	2.31
(b)-(a) ..	250-500	-0.74	-0.91	+42	+22.5	-11	+0.7	-1.33	+0.16
	2.5-5.0	-0.32	-0.41	+18	+8.8	+1	+0.5	-0.48	+0.24

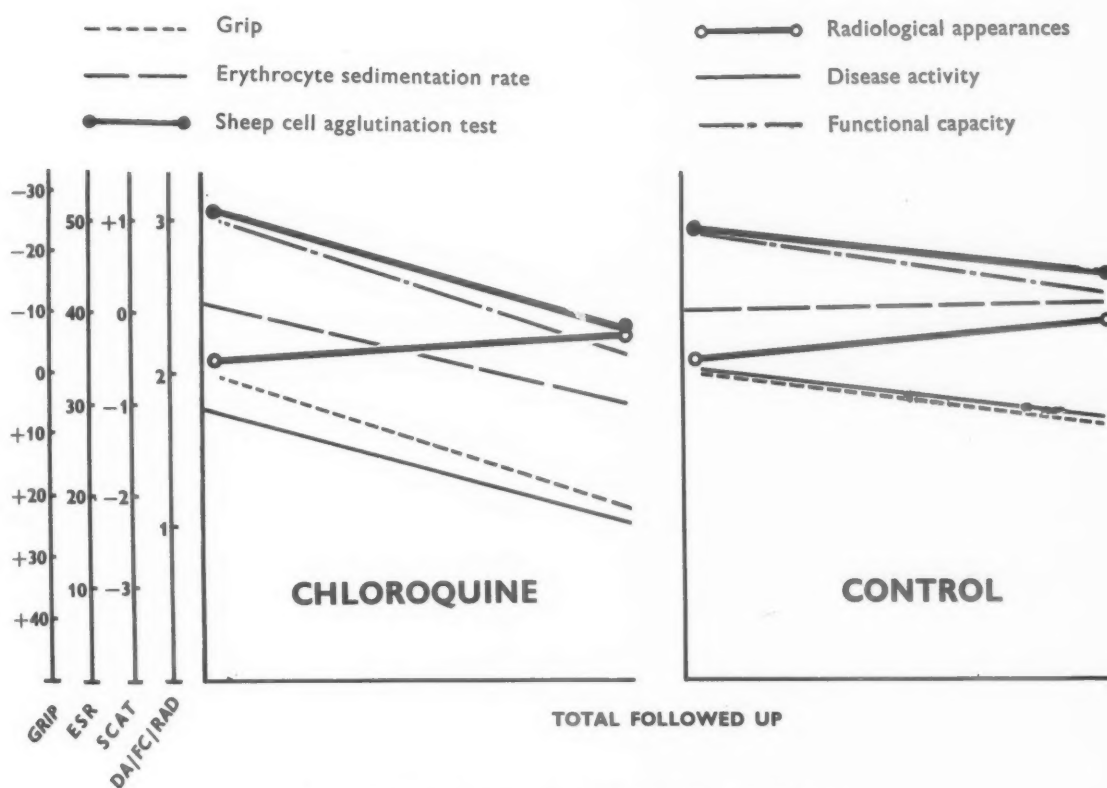


Fig. 4.—Diagrammatic representation of the data in Table VIII.

Radiological Changes.—The x-ray changes in the hands and feet taken at entry and at follow-up were all read in consecutive sessions by one observer (A.J.P.) who was unaware at the time of the treatment each patient had received. The films were assessed for osteoporosis, erosion of bone, narrowing of joint space, and subluxations, and an overall grading was made for the severity of rheumatoid changes. A detailed analysis of the results in all

patients with disease of 3 to 24 months' duration is shown in Table IX (overleaf). The results in the SCAT-positive patients and in the total sample followed up were also analysed; these are not shown in detail, but the mean gradings for rheumatoid appearances at entry and at follow-up, and their changes over this period, are shown in Tables VI, VII, and VIII, and illustrated in Figs 2 to 4. In many cases the degree of change, although definite, was insufficient

TABLE IX

NUMBER OF PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION WITH GIVEN GRADES OF RADIOLOGICAL CHANGES IN FILMS OF HANDS AND FEET

Site	Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Grade					Total X-rayed	Not X-rayed	Change in Grade				Deterioration or Improvement		
			0	1	2	3	4							(b)-(a)		
										+2	+1	±0	-1	Deteriorated	No Change	Improved
Hands	(a) Entry ..	250-500 2.5-5.0	3 5	7 3	10 9	4 1	—	24 18	2 3							
	(b) After 1 yr ..	250-500 2.5-5.0	3 4	4 1	11 10	5 3	1 —	24 18	2 3	1 2	4 3	19 12	— 1	14 12	8 4	2 2
Feet	(a) Entry ..	250-500 2.5-5.0	7 4	9 7	6 6	1 —	1 1	24 18	2 3							
	(b) After 1 yr ..	250-500 2.5-5.0	6 3	5 5	10 7	3 2	— 1	24 18	2 3	2 —	4 6	16 12	2 —	13 11	9 7	2 —

Grade: 0 = None 1 = Doubtful 2 = Slight 3 = Moderate 4 = Severe.

to alter the absolute grading for severity of rheumatoid appearances; a statement regarding improvement or deterioration could, however, be made, and Table IX also contains the results of this analysis.

At follow-up there had been a slight but definite progression of radiological change in both the treated and the control groups, but there was no significant difference in the rate of progression of radiological changes in the two groups. The numbers of patients whose films showed given grades of abnormality were remarkably similar in the two groups both at entry and at follow-up; the numbers of patients whose films showed given grades of improvement or deterioration were also similar. Improvement in the radiological appearances was seen in only four patients, of whom two were in the treated and two in the control group; in no case was there any definite evidence that treatment with chloroquine had influenced the rate

of progression of the radiological joint changes.

About three-quarters of the x-ray films were read independently by a second observer (K.A.E.M.); although there were slight differences in the scores recorded for each feature by the two observers, there was no important disparity between them, and in every case changes in grade were recorded in the same direction.

Results of Sheep Cell Agglutination Test (SCAT).—

The tests were done by Ball's method (Ball, 1950; Kellgren and Ball, 1959). In order to facilitate comparison, the results are expressed in the same manner as in the report of the prednisolone/analgesics trial: the minimal positive titre of 1 in 32 is taken as zero, and dilutions above and below this are scored as +1, +2, etc., and -1, -2, etc. The results for all patients with disease of 3 to 24 months' duration are shown in detail in Table X.

TABLE X

RESULTS OF SHEEP CELL AGGLUTINATION TESTS* IN PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Results of Tests							Total	Changes in Results of Tests (b) - (a)				
		Negative			Positive					+4 to +3	+2 to +1	±0 to -1	-2 to -3	-4 to -5
		-4 to -3	-2 to -1	Total	0 to +1	+2 to +3	+4 to +5	Total						
(a) Entry	250-500 2.5-5.0	5 5	3 1	8 6	6 4	5 10	7 1	18 15	26 21					
(b) After 1 yr	250-500 2.5-5.0	9 7	5 —	14 7	6 5	5 5	1 4	12 14	26 21	— —	1 6	9 12	14 3	2 —

* Based on minimal positive titre = 0, with deviations above and below in numbers of tubes showing agglutination.

The mean SCAT titre at entry into the trial was higher in the treated than in the control group. On follow-up, however, there was a striking change: the number of patients showing positive tests had fallen from eighteen to twelve in the treated group, but only from fifteen to fourteen in the controls. In the treated patients the titre had fallen in sixteen and had increased in only one, whereas in the control group the titre had fallen in only three and had increased in six: the greater fall in the mean titre in the treated group is highly significant ($p < 0.001$).

Separate analysis of the SCAT-positive patients (Tables VI and VII) and of all patients followed up (Table VIII) reveals a similar trend: the mean SCAT titres were higher in the treated group at entry but showed a greater fall at follow-up than the control group: the greater fall in the treated group was highly significant in the SCAT-positive patients with disease of short duration ($p < 0.001$) and in all patients followed up ($p < 0.01$), though not in the SCAT-positive patients with disease of long duration.

The SCAT results are therefore in accord with the

changes in the clinical status and the erythrocyte sedimentation rate, the treated patients showing greater improvement.

Correlation of Changes in SCAT Titre with Changes in Other Characteristics.—Fig. 5 shows the percentage changes in grip strength plotted against changes in SCAT titre for all patients who were SCAT-positive at entry. In both the treated and the control patients decrease in SCAT titre is associated with increase in grip strength and *vice versa*; the correlation coefficient ($r = 0.40$), while not showing very close functional relation of the two characteristics, is significant ($p < 0.001$). Treated and control patients do not overlap closely, the treated patients spreading more to the upper right, the control patients more to the lower left in the figure; this, however, is due not solely to the differences in treatment but also to the fact that there was a greater proportion of patients with disease of short duration in the treated group; it is evident from the data given earlier that such patients in either treatment group did better than those with disease

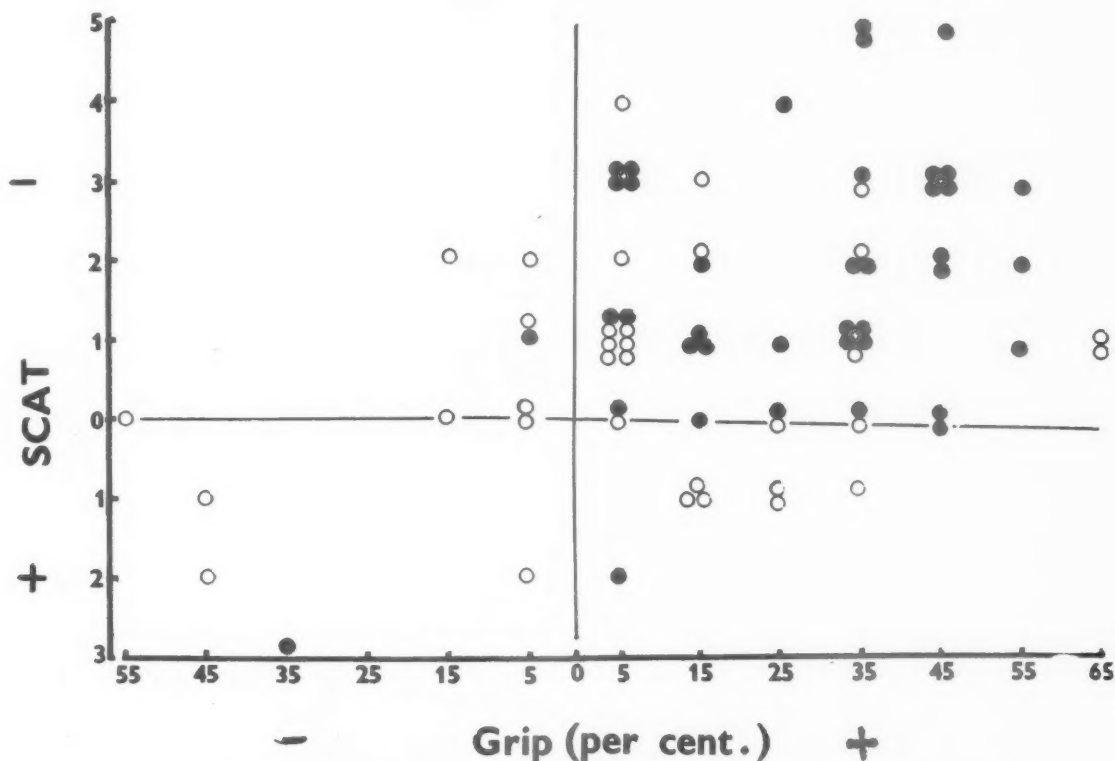


Fig. 5.—Correlation between SCAT results and grip in SCAT-positive patients with disease of any duration.
Black circles = Chloroquine-treated patients.
Hollow circles = Control patients.

of long duration. For the same reason it is not surprising that the correlation coefficient for the control group separately ($r = 0.23$) does not differ significantly from zero in this small sample, whereas for the treated group the correlation is still significant ($r = 0.40$).

An attempt was made to express by a single figure (composite score) the "change in clinical state" of the patient. The value chosen was the sum of the changes in functional capacity, disease activity, sedimentation rate, and grip strength, the values for each of these being scaled to give approximately equal weight to each characteristic.*

In Fig. 6 the "change in clinical state" of those patients who were SCAT-positive at the start of the trial is plotted against the change in SCAT-titre. The picture is very similar to that in Fig. 5, improvement in clinical state being generally

associated with a fall in SCAT titre and deterioration with a rise.

In treated and control patients combined, the correlation coefficient was 0.35, which was significant ($p < 0.01$). In the treated group by itself the correlation coefficient was 0.58 ($p < 0.001$) and in the control group it was only 0.16, but the inequality of the proportions of patients with disease of long and short duration again probably accounts for some part of the difference between the two groups; the overall picture leaves little doubt that in the treated group clinical improvement tended to be accompanied by a decrease in the SCAT titre.

The possibility that chloroquine in the serum might influence the SCAT and so produce spuriously low titres was investigated. The highest serum concentration observed with doses of 500 mg. is between 150 and 250 $\mu\text{g.}$ per litre (Alving, Eichelberger, Craige, Jones, Whorton, and Pullman, 1948); it was found that the addition *in vitro* of chloroquine diphosphate to give a concentration of either 1,000 or 10,000 $\mu\text{g.}$ per litre in the serum did not alter the SCAT titre (Ball, 1960).

* Changes in grades of disease activity and functional capacity, and 1/10 each of changes in grip (per cent. of higher reading) and erythrocyte sedimentation rate (mm./hr), added together and divided by 4.

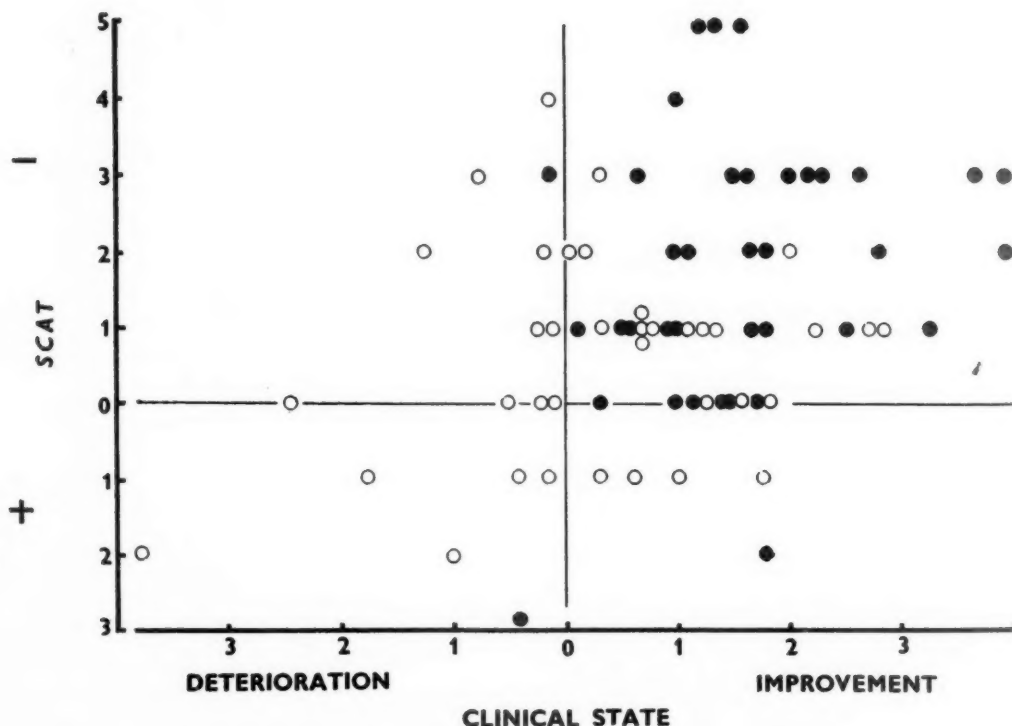


Fig. 6.—Correlation between SCAT results and clinical state in SCAT-positive patients with disease of any duration.
Black circles = Chloroquine-treated patients.
Hollow circles = Control patients.

Discussion

The results of this trial, which are in accord with the recent report by Freedman and Steinberg (1960), suggest that treatment with chloroquine diphosphate in doses of 250 to 500 mg. daily is beneficial in rheumatoid arthritis, particularly if the duration of the disease is less than 2 years, although it does not influence the progression of radiological changes in the first year of observation.

These findings are particularly interesting when compared with the results of the prednisolone/analgesics trial conducted by the Joint Committee of the Medical Research Council and Nuffield Foundation (1959, 1960), in which treatment with prednisolone was associated with significantly less increase of radiological changes in the joints and greater improvement in all clinical and laboratory characteristics studied except the sheep cell agglutination titre, which more often increased in the prednisolone-treated patients, especially during the first 2 years of the trial.

In the present trial, treatment with chloroquine was associated with a significant improvement in terms of the clinical and laboratory characteristics and also with a significant decrease in SCAT titres: progression of radiological changes, however, appears not to have been influenced. It has been suggested, on the basis of the results in the prednisolone/analgesics trial, that the processes responsible for joint erosion and for production of the rheumatoid serum factor might not be identical, since prednisolone appeared to suppress the former while enhancing the latter; the findings in the present trial are compatible with this interpretation, since chloroquine appears to favour regression of the serological changes while having no influence on joint erosion in a one-year period.

The observations of de Forest, Mucci, and Boisvert (1958) provided evidence that the titre of the agglutinating factor might be of prognostic significance, since the trend of the titres over a 2-year period was found to reflect the clinical course of the disease; remission was generally associated with reversion of the test from positive to negative, and continued positivity, usually in moderately high titres, with progressive disease. The results in our patients support this evidence, since clinical improvement was correlated with a decrease in SCAT titre; it therefore seems reasonable to infer that a decrease in SCAT titre is to the advantage of the patient.

Toxicity was not a great problem: although the total incidence of symptoms which might have been due to the treatment appears high (19.1 per cent.) no serious toxic effects were encountered.

The incidence of toxic effects is similar to that reported by Merkel (1959) who used the same order of dosage and observed a similar spectrum of symptoms: in ninety of the patients treated with doses of 250 to 500 mg. diphosphate daily the total incidence of toxic symptoms was 22 per cent. Cohen and Calkins (1958) found a higher incidence: twelve of 21 patients given 250 to 500 mg. daily had symptoms attributed to the toxic effect of the drug, and in seven the treatment had to be withdrawn: one patient developed a bizarre psychosis, with delusions and euphoria, but recovered when chloroquine was withheld. Cohen and Calkins point out that their patients were specifically questioned concerning the known toxic manifestations of the drug and suggest that this may have contributed to the high incidence of minor symptoms; the present trial differed from that of Cohen and Calkins in this respect, since no systematic enquiry at regular short intervals was made. Some toxic effects reported previously were not observed in this series; in particular, bleaching of the hair (Sharvill, 1955), urticaria, alopecia, and exfoliative dermatitis (Scherbel and others, 1958), conjunctivitis and precordial pain (Stuart and Aukland, 1958) were not observed: most of these effects, and in addition visual disturbance due to difficulty with accommodation and diplopia, and slight loss of weight, had previously been described by Alving and others (1948). Leucopenia (Cohen and Calkins, 1958) was not observed in our patients, but white blood counts were not done routinely.

Perhaps the most important toxic effects, from the practical standpoint, are those recently reported to affect the eye. Hobbs and Calnan (1958) drew attention in patients treated with chloroquine to the development of deposits in the corneal epithelium; these were similar to those described by Mann (1947) in workers engaged in the manufacture of mepacrine, but their nature was undetermined. Out of a selected group of 28 patients to whom chloroquine was being administered for various indications, 22 had corneal changes, but there was no obvious relationship between dosage or duration of treatment and the development of keratopathy; in some patients the changes were noted to have disappeared after chloroquine treatment had been discontinued. A pathognomonic symptom of these corneal changes is the spontaneous perception of coloured haloes around bright lights, but this was noticed only by three of the patients in Hobbs and Calnan's series and by none in the present study. Zeller and Deering (1958) reported ten similar cases in which regression of the changes followed cessation of treatment. These

corneal deposits are visible only on slit-lamp examination, and this was not carried out routinely in our patients, so that we cannot state whether asymptomatic corneal changes occurred. Kersley and Palin (1959) reported an incidence of keratopathy of 47 per cent. in 36 patients treated with hydroxychloroquine in doses of 400 mg. daily or more, but in all cases the changes had disappeared within 6 months of stopping treatment. A different type of corneal reaction to antimalarial compounds has also been reported; Reese (1946) described an acute congestive reaction resulting in oedema, associated with transient blurring of vision, in airmen receiving mepacrine in suppressive doses, and a comparable experience was reported by Bleil (1958) as part of a severe toxic reaction to amodiaquine: this type of reaction has not been reported in patients treated with chloroquine. A third type of visual disturbance is mentioned by Hobbs and Calnan in which the patients, usually hypermetropes, complained of transient blurring of vision and difficulty with focusing; these symptoms arose either when treatment was started or when the dose was increased, and were attributed to temporary impairment of ciliary function as part of a general disturbance caused by incomplete tolerance of the drug, an effect which is seen also with other drugs such as the sulphonamides. Two treated patients in the present trial had symptoms of dizziness and visual disturbance of this latter type, after less than 2 weeks' treatment with two tablets daily: their symptoms ceased within a few days of stopping treatment. Cataract has not been reported as a complication of chloroquine treatment, and in the absence of further data it must be assumed that its occurrence in one treated and one control patient in this trial was coincidental. It is possible, however, that more serious effects on the eye may attend prolonged treatment; Hobbs, Sorsby, and Freedman (1959) described three cases in which retinopathy with macular degeneration and persisting impairment of vision followed treatment with chloroquine in doses ranging from 100 to 600 mg. daily: this is the most serious toxic effect which has yet been reported and clearly requires further study, although vision has improved in two of the three cases since chloroquine was withdrawn (Freedman, 1960).

Conclusion

The results of this trial suggest that treatment with chloroquine may be of some value in rheumatoid arthritis. Few serious and no irreversible toxic effects were observed, and in this respect chloroquine compares favourably with corticosteroids and gold; the risks of complications such as retinal damage

require further investigation, but from the experience of this trial it seems unlikely that such toxic effects will occur frequently if the dose of chloroquine does not exceed 250 mg. of the diphosphate (150 mg. of the base) daily.

It is disappointing that the treatment did not influence the progression of joint damage shown radiologically, but the greater improvement in other respects in the patients given chloroquine appears to warrant its use as a supplement to conservative measures. It would also appear that a decrease in the sheep cell agglutinating titre may be correlated with clinical improvement. If it is confirmed that corticosteroid treatment results in a tendency for the SCAT titre to rise, or to fall less than in controls, and if it is accepted that this represents a disadvantage, it would not be unreasonable to give chloroquine concurrently when corticosteroids have to be used; the effects of corticosteroids on the agglutinating titre might then be counteracted. It also seems possible that adequate suppression of symptoms might be maintained with smaller doses of corticosteroids if chloroquine were given at the same time; it has not yet been shown that the two types of compound would act in synergism, but there seems no reason to suppose that they would not do so or that they would act antagonistically.

Finally, chloroquine has the advantage over gold of being easily administered, while supervision of the treatment need cause the general practitioner little anxiety.

Summary

The results are reported of a long-term, controlled, double-blind therapeutic trial of chloroquine in 134 patients with rheumatoid arthritis.

Alternate patients were treated with one tablet daily (two tablets while in hospital) each containing either 250 or 2.5 mg. chloroquine diphosphate, as an adjunct to a conservative regime; gold was not given, but 21 patients also received corticosteroids.

The results of clinical, laboratory, and radiological assessments at entry are compared with those at follow-up after 1 to 2 years' treatment.

Patients treated with 250 mg. tablets showed significantly greater improvement, in terms of clinical and laboratory criteria, than controls; a similar degree of progression of disease was seen radiologically in both groups.

There was a significant correlation between decrease in the sheep cell agglutinating titre and clinical improvement.

Thirteen treated patients and ten controls had symptoms ascribed to chloroquine toxicity; seven treated patients and one control discontinued

chloroquine treatment after less than 6 weeks for this reason.

It is concluded that chloroquine may be of some value as an adjunct to the conservative treatment of rheumatoid arthritis.

We are greatly indebted to Prof. J. H. Kellgren for advice on the planning and management of this trial, which was carried out on patients under his care, and to Dr. J. Ball for the sheep cell agglutination tests. We also record our thanks to Dr. L. J. Atkinson and Dr. K. D. Coorey, who carried out a number of the assessments, to the Nursing Staff of the Manchester Royal Infirmary and Devonshire Royal Hospital, Buxton, and the secretarial staff of the Rheumatism Research Centre. We are also grateful to Dr. J. M. Mungavin, of the Imperial Chemical Industries Pharmaceutical Division, for arranging the supply of specially prepared chloroquine tablets.

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APPENDIX

Details of the Twelve Patients not Followed-up

Died.—Two patients died early in the trial.

One was a female aged 72 in the control group, who had SCAT-positive rheumatoid arthritis of one year's duration superimposed on long-standing generalized osteo-arthritis. Conservative treatment in hospital was ineffective, and prednisolone was therefore added in a dose of 10 mg. daily. Following an initial improvement, she developed intestinal obstruction, pyelonephritis, and pneumonia, and died 5½ months after entry into the trial.

The second death was that of a female aged 34 in the treated group, who had SCAT-positive rheumatoid arthritis of 10 years' duration and also otosclerosis; she had been subject to attacks of depression for several years. After some initial improvement she had a recurrence of her depression and committed suicide 6 months after entry into the trial.

Not Traced or Refused to Attend.—Four such patients were lost to follow-up.

One was a female aged 51 in the treated group, with SCAT-positive arthritis of 9 years' duration; she received treatment as an in-patient for 5 weeks and seemed to be making satisfactory progress on discharge, but did not attend for follow-up and could not be traced.

The second was a female aged 61 in the treated group, with SCAT-positive arthritis of 1 year's duration, who had shown some improvement after 4 weeks' treatment as an in-patient; she did not attend for follow-up, but in answer to a postal inquiry replied that there had been no change in her condition and that she was not taking any special tablets.

The third was a man aged 59 in the control group, with advanced SCAT-positive arthritis of 11 years' duration, who started treatment after undergoing arthroplasty of the left hip and arthrodesis of the left knee. His disability was chiefly due to destructive changes in the joints, and only limited rehabilitation was achieved: he did not attend for follow-up and wrote to say he had ceased taking the tablets soon after he had returned home.

The fourth was a female aged 66 in the control group, with SCAT-positive rheumatoid arthritis of 18 months' duration superimposed on generalized osteo-arthritis, who received 7 weeks' treatment as an in-patient. Little progress was achieved with conservative treatment and prednisolone was added to the regime with improvement, though she remained much disabled. She did not attend for follow-up, and postal inquiry elicited no reply.

Exclusion for Other Reasons.—Six patients who were withdrawn from the trial after the initial assessment were not subjected to formal follow-up.

A female in the treated group, aged 32, with SCAT-positive arthritis of 2½ years' duration, started treatment as an in-patient; after 5 days she complained of severe dizziness on sudden movements of the eyes and head, but there were no objective neurological signs and the symptoms subsided within 2 days of ceasing treatment. In spite of prolonged conservative treatment, with the addition of prednisolone in low dosage, her symptoms have remained severe; when seen a year after entry to the trial there was evidence of widespread active arthritis and she was considerably disabled.

In two patients there was confusion over the treatment. A man aged 61, with very mild SCAT-positive arthritis of 1 year's duration, started treatment with control tablets as an in-patient, but was shortly afterwards transferred to the care of another physician; treatment with chloroquine was continued, but it is not certain whether the specially-prepared control tablets or the ordinary commercial preparation was used. This man's disability was due largely to a severe compensation neurosis and at entry his arthritis showed little activity; when he was seen a year after entry there was no objective sign of active arthritis. A female aged 56, with SCAT-negative arthritis of 10 months' duration, received control tablets as an in-patient, and after 3 months of conservative treatment her arthritis had passed into complete remission; 8 months after entry she was still almost free of symptoms, but it emerged that she had for some months been taking chloroquine prescribed by her general practitioner instead of the control tablets. A year after entry her condition remained generally satisfactory though there had recently been a mild recurrence of symptoms in the knees and feet.

A female, aged 45 in the treated group, was originally diagnosed as having advanced nodular rheumatoid arthritis but later her illness developed the features of systemic lupus erythematosus; corticotropin was given together with chloroquine from the beginning, and for a year she did well but then relapsed; prednisolone was later substituted for corticotropin with great symptomatic benefit.

A female aged 68 in the treated group, with SCAT-positive arthritis of 20 years' duration, started treatment as an in-patient, but it soon became apparent that she was suffering from a mild psychosis which had in fact been present before treatment was started. Since she showed paranoid features it was thought wiser, after 10 days, to withdraw her from the trial. Her mental state was apparently unaffected by the treatment; no follow-up was attempted.

A female aged 42 in the treated group, with nodular rheumatoid arthritis of 17 years' duration, started treatment as an in-patient. She was severely disabled by destruction of the hip joints, her disease generally appearing quiescent: chloroquine was discontinued a few weeks after her transfer to the care of an orthopaedic surgeon. During the succeeding 2 years there has been a slight increase in her various deformities.

Discussion.—DR. B. ANSELL (*Taplow*) commented on three corneal opacities seen in the first ten patients treated with chloroquine and two incidents of hair bleaching, and asked for information on the incidence of these in the trials.

She then reported the results of a small trial conducted by Dr. E. B. D. Hamilton at Taplow and Dr. J. T. Scott at Hammersmith. 32 patients had completed a 6-month trial, during which they received 600 mg. Plaquenil daily for 3 months and 1 mg. Plaquenil daily for 3 months. In addition there had been three withdrawals, two cases of dyspepsia (one being on placebos at the time), and one of deterioration requiring steroids. Only one instance of visual disturbance (zigzagging of light) had been seen in this trial.

Both subjectively and objectively improvement was slightly greater during the treatment period.

DR. POPERT replied that he had not seen bleaching or loss of hair as a complication, but the patients in the Manchester series had received a lower dosage of chloroquine.

DR. R. M. MASON (*London*) asked how long it took to obtain improvement, and Dr. Popert replied that their impression was that 3 to 6 months' treatment was needed.

DR. G. D. KERSLEY (*Bath*) reported that amodiaquine (camoquin) appeared more toxic than hydroxychloroquine (plaquenil). Improvement was seen after one month, and relapse after stopping therapy in about the same time. Corneal opacities had been noted in 35 per cent. of the patients, but these had cleared in 1 to 4 months after withdrawal of the drug. 10 per cent. of the patients had complained of mistiness of vision but no retinal changes had been observed. One fatal case of agranulocytosis with camoquin had been seen.

PROF. S. J. HARTFALL (*Leeds*) asked for some information concerning the different preparations of antimalarial drugs, and also expressed concern about the unknown influence of placebo reactors in clinical trials.

DR. A. J. POPERT replied that chloroquine diphosphate 250 mg., chloroquine sulphate 200 mg., and hydroxychloroquine sulphate 200 mg. were equivalent in terms of chloroquine base content. There was no evidence that they differed in antimalarial potency or that one salt was more effective than another.

DR. A. FREEDMAN (*London*) said that he was pleased to learn from the Manchester clinical trial that 250 mg. chloroquine diphosphate had proved effective; he thought that this lower dosage, compared with the 400 mg. chloroquine sulphate he had used initially, probably accounted for the absence of corneal opacities.

DR. MCEWEN (*Melbourne*) said that if dosage was expressed in terms of chloroquine base it would eliminate the present confusion concerning preparations and dosage.

DR. R. M. MASON (*London*) said that his unit was studying placebo reactors in a current trial. They had also found that there were quite a proportion of patients in both groups who did not take the tablets and he thought that that might dilute the results.

PROF. J. H. KELLGREN (*Manchester*) wondered whether antimalarials might interfere directly with the sheep cell agglutination titre.

DR. J. BALL (*Manchester*) said that, at the plasma concentrations used, there was no effect *in vitro*.

DR. W. R. M. ALEXANDER (*Edinburgh*) asked whether other antimalarials, of different chemical composition, were being tried. Was the effect dependent on antimalarial action or chemical composition.

DR. POPERT replied that the 4-aminoquinolines, chloroquine and hydroxychloroquine, and also mepacrine, had mainly been used. Mepacrine bore some relation chemically to chloroquine, and could be regarded as a 4-aminoquinoline with an extra benzene ring attached to the quinoline nucleus. He did not think that the 8-aminoquinolines, such as pamaquine and primaquine, had been used, since they were considerably more toxic; nor had Proguanil, which had quite a different structure.

DR. A. FREEDMAN (*London*) observed that in a screening programme of the effects of many agents on the pleuropneumonia-like arthritis in rats, only three were found to have any effect. These were aureomycin, quinacrine, and gold.

Diphosphate de chloroquine dans l'arthrite rhumatismale. Un essai contrôlé

RÉSUMÉ

On rapporte les résultats d'un essai thérapeutique contrôlé (par la méthode de *double-blind*) et prolongé de la chloroquine chez 134 malades atteints d'arthrite rhumatismale.

Des malades pris alternativement, reçurent un comprimé (ou deux s'ils étaient hospitalisés) par jour, contenant 250 mg. de diphosphate de chloroquine pour les uns et 2,5 mg. pour les autres. De plus, tous les malades étaient soumis au traitement habituel; aucun ne reçut de sels d'or, mais 21 d'entre eux reçurent des corticostéroïdes.

Les résultats des examens médicaux, radiologiques et de laboratoire au début de l'essai ont été comparés à ceux obtenus après d'un à deux ans de traitement.

Les malades traités par les comprimés de 250 mg. ont accusé une amélioration appréciablement plus grande, du point de vue médical et analyse, que les témoins; le tableau radiologique était le même dans les deux groupes.

On nota une corrélation significative entre la baisse

des titres d'agglutination des globules de mouton et l'amélioration physique.

Des symptômes attribuables à la toxicité de la chloroquine se sont manifestés chez treize malades traités activement et chez dix témoins; sept malades du groupe traité activement et un malade du groupe témoin ont abandonné la chloroquine au cours des six premières semaines en raison de ces symptômes.

On conclut que la chloroquine présente une certaine valeur comme adjuvant dans le traitement habituel de l'arthrite rhumatismale.

Difosfato de cloroquina en la artritis reumatoide

SUMARIO

Se relatan los resultados de una prueba ciega de tratamieto a largo plazo con cloroquina en 134 enfermos con artritis reumatoide.

Enfermos alternativos fueron tratados con una pastilla diaria (dos pastillas mientras estuvieron hospitalizados) conteniendo sea 250, sea 2,5 mg. de difosfato de cloroquina, como coadyuvante de un tratamiento conservativo; ninguno de los enfermos recibió sales de oro, pero 21 de ellos fueron tratados a la vez con corticosteroides.

Los resultados de las investigaciones clínicas, radiológicas y de laboratorio al principio de la prueba se compararon con los obtenidos después de uno a dos años de tratamiento.

Los enfermos tratados con pastillas de 250 mg. del fármaco presentaron una mejoría significativamente mayor, desde los puntos de vista clínico y de laboratorio, que los testigos; el mismo grado de progresión radiológica de la enfermedad apareció en ambos grupos.

Se registró una significativa correlación entre la disminución en los títulos de aglutinación de los eritrocitos de carnero y la mejoría clínica.

Síntomas atribuibles a la toxicidad de la cloroquina aparecieron en trece de los enfermos tratados y en diez de los testigos; siete de los enfermos en tratamiento activo y uno del grupo de control abandonaron el tratamiento con cloroquina por dicha razón durante las seis primeras semanas.

Se concluye que la cloroquina puede ser de valor como coadyuvante del tratamiento conservativo de la artritis reumatoide.

QUANTITATIVE AND QUALITATIVE ANALYSIS OF JOINT STIFFNESS IN NORMAL SUBJECTS AND IN PATIENTS WITH CONNECTIVE TISSUE DISEASES*†

BY

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Rheology is the study of the deformation and the flow of matter. In the present communication this science is applied to the human joint, its motion, and the forces resisting joint motion.

The techniques used to measure joint stiffness have long been used by physicists, physical chemists, and engineers in studying the stiffness of a wide range of materials. Such studies have been of particular use in two areas: They have provided a quantitative measure of stiffness in precise physical terms, and they have defined qualitatively the different parameters contributing to total stiffness. This latter type of analysis has been important, for example, in studies of the cross-linking in elastic polymers.

Both types of study have been employed in this investigation. Rheological techniques have been used to measure alterations in joint stiffness produced by physiological changes, pathological disorders, and therapeutic methods, and it is expected that a detailed study of the parameters contributing to total stiffness will give information on alterations in the materials of which joints are made.

Methods

The apparatus used has been described in detail elsewhere (Wright and Johns, 1960a). In principle, the force required to impose a given motion on the joint was recorded; this was the force required to overcome joint stiffness. The second metacarpophalangeal joint was moved sinusoidally at various amplitudes and frequencies of rotation. The torque (in gram-centimetres) required to impose this motion was displayed

on both vertical axes of a dual beam cathode ray oscilloscope. The amplitude of rotational displacement (in radians) was displayed on the horizontal axis of one beam, and the rotational velocity (in radians per second) on the horizontal axis of the other beam. Loops relating torque to displacement and torque to velocity were thus traced on the oscilloscope, and representative displays were photographed.

These data were obtained in part by using the apparatus originally described in which the sinusoidal motion was derived from a pendulum, and in part by a crank driven by a variable speed motor (Fig. 1). This modification permitted investigation of a wider range of frequencies (0.003 to 3 cycles per second), velocities (15 radians per second, maximum), and accelerations (280 radians per second², maximum).

Great care was taken in aligning the axes of rotation of the joint and the apparatus. Alignment was facilitated by an indicator extending from the finger holder to the axis of rotation of the finger (Fig. 2). Any toggle action was shown by the needle moving off centre, its tip being stationary when the joint was perfectly aligned. When these precautions were taken reproducibility of results was good. Measurements from series of records taken without moving the hand had a coefficient of variation of ± 1.5 per cent. When the hand was removed from the apparatus and then replaced measurements showed a coefficient of variation of ± 3.9 per cent.

Theoretical Considerations

Five types of stiffness were studied: elastic, viscous, inertial, frictional, and plastic.

(1) An elastic substance is one in which the stress (deforming force, or in this instance torque) is a function of the strain (deformation, or in this instance rotation). This is exemplified by an ideal spring in which the relationship is linear (Hookean, Fig. 3a), or by a rubber band in which the relationship is non-linear (non-Hookean, Fig. 3b). The slope of the line relating torque and rotational displacement measures the elastic stiffness (gram-centimetres/radian).

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† Presented in part at a meeting of the Heberden Society on July 2, 1960.

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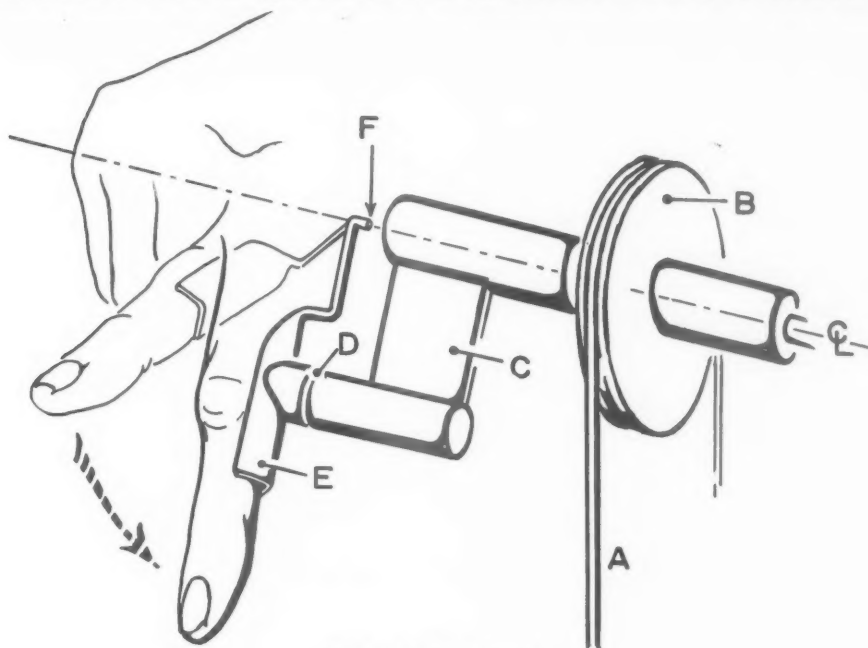


Fig. 1.—Modified apparatus:

- A. Cable driven sinusoidally by a crank.
- B. Pulley converting motion to sinusoidal rotation.
- C. Lever transmitting torque to finger and on which strain gauges are bonded.
- D. Swivel.
- E. Finger holder.
- F. Centre indicator.

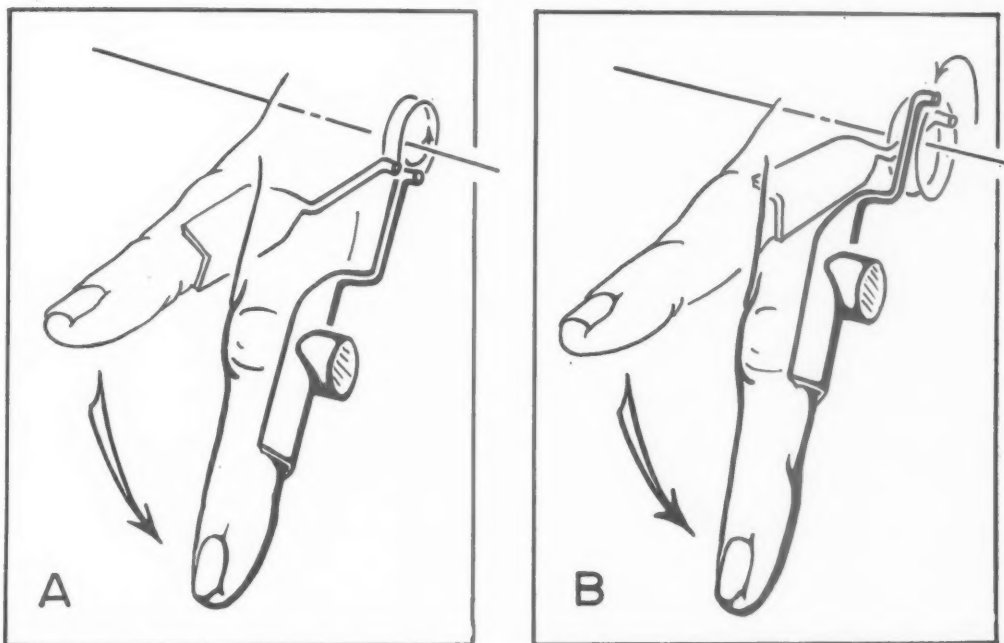


Fig. 2.—Centre indicator. The finger holder was removed from the apparatus and attached to the finger in such a position that the indicator tip was not displaced as the joint rotated. Holder rotates as in A when distally placed, and as in B when proximally placed.

The holder was then attached to the apparatus and the hand so positioned that the indicator of the joint axis and that of the apparatus coincided.

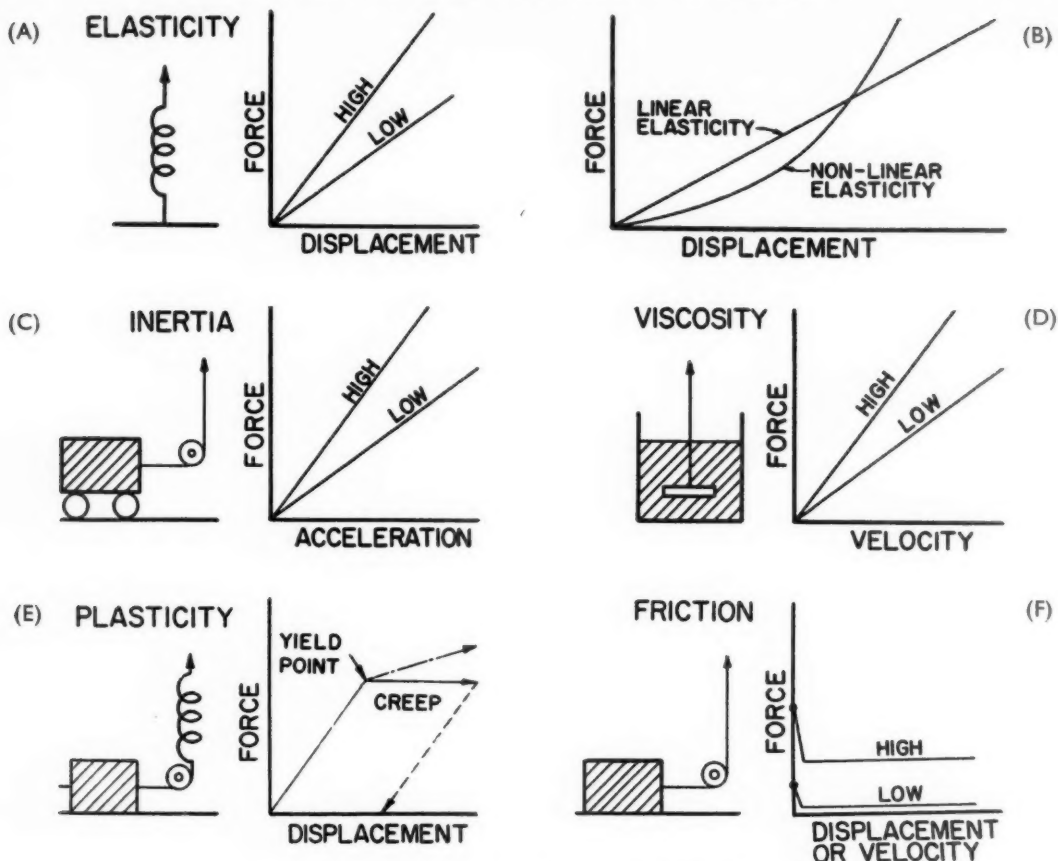


Fig. 3.—Force relationships in five types of stiffness.

- A. Elastic stiffness exemplified by an ideal spring, showing a linear relation between force and displacement. A stiffer spring exhibits a greater stiffness (steeper slope).
- B. Linear and non-linear elasticity in which stiffness (slope) increases with displacement.
- C. Inertial stiffness exemplified by a mass moving on frictionless bearings, showing a linear relation between force and acceleration.
- D. Viscous stiffness exemplified by a plate moving through an ideal viscous fluid, showing a linear relation between force and velocity. Increased viscosity results in greater viscous stiffness (steeper slope).
- E. Plastic stiffness illustrated by a spring attached to a frictional element. The yielding behaviour is described in the text.
- F. Frictional stiffness exemplified by two opposing surfaces. The force is independent of displacement or velocity and is greatest at rest.

(2) A viscous substance is one in which the stress (torque) is a function of the velocity. This is exemplified by a plate moving through an ideal viscous substance (Fig. 3d); the slope of the line relating torque and velocity measures the viscous stiffness (gram-centimetres/radian per second). There are both linear (Newtonian) and non-linear (non-Newtonian) cases.

(3) Inertial stiffness is exemplified by a mass moving on frictionless bearings (Fig. 3c). The force producing the motion is a function of the acceleration, and inertial stiffness is in this instance measured in terms of gram-centimetres/radian per second².

(4) Torques due to frictional stiffness (Coulomb friction) are independent of displacement and velocity (Fig. 3f). Such stiffness is exemplified by a block moving over a rough surface. Engineers frequently

refer to a velocity dependent friction, lubricated friction. This is a combination of Coulomb friction and viscosity.

(5) Plastic stiffness is the most difficult to appreciate intuitively. This yielding or doughy stiffness may be exemplified by a St. Venant body, a spring connected to a block resting on a surface (Fig. 3e). As force is increased the spring elongates, and there is elastic behaviour up to a certain point (the yield point). With further displacement or with further application of force the block slides and there is progressive displacement with constant force (creep). Removal of the force is accompanied by only partial return to the initial displacement (broken line, Fig. 3e). This is termed incomplete strain recovery. Real substances with plasticity usually exhibit viscous properties above the yield point (dash and dotted line, Fig. 3e) as if a viscous element was attached to the left of the block.

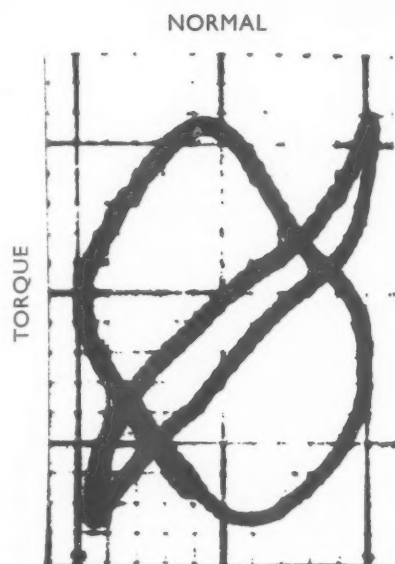


Fig. 4.—Normal record. The elliptical tracing relates torque to velocity (abscissa). The sigmoid curve exhibiting hysteresis relates torque to displacement (abscissa). Flexion is to the right.

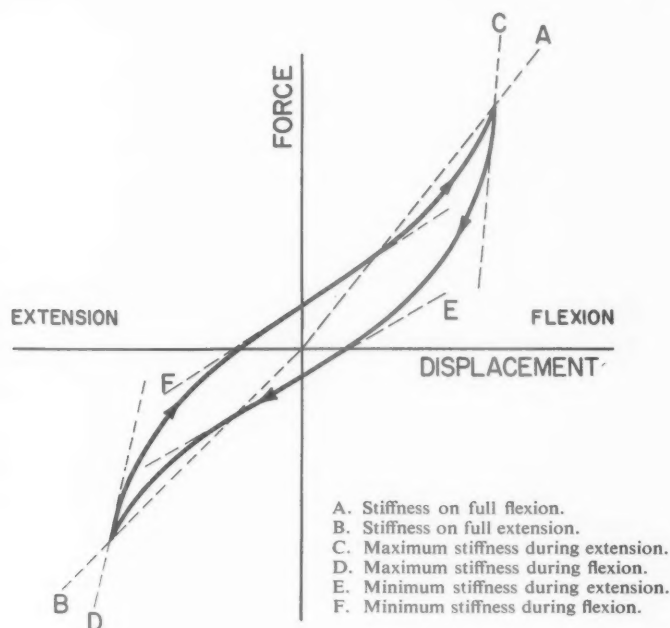


Fig. 5.—Diagram of joint stiffness showing slopes measured (broken lines).

Results in Normal Subjects

A tracing relating torque and rotation from which elastic stiffness could be determined is shown in Fig. 4. The elasticity was non-linear in character. That the tracing was a loop and not a line was due to the presence of viscous and plastic stiffness.

The slopes (gram-centimetres/radian) at full flexion and extension were measured by the slopes of the lines connecting the points of maximum amplitude with the origin (Fig. 5, Slopes A and B).

As will be discussed, further studies revealed that this stiffness at maximum amplitude could not be ascribed entirely to elastic effects. So while these slopes provided a convenient index of elastic stiffness (steeper slopes indicating greater stiffness), they will be called stiffness at maximum flexion or extension rather than elastic stiffness at flexion or extension.

Measurements showed that elastic stiffness increased significantly at greater amplitude of rotation (Fig. 6).

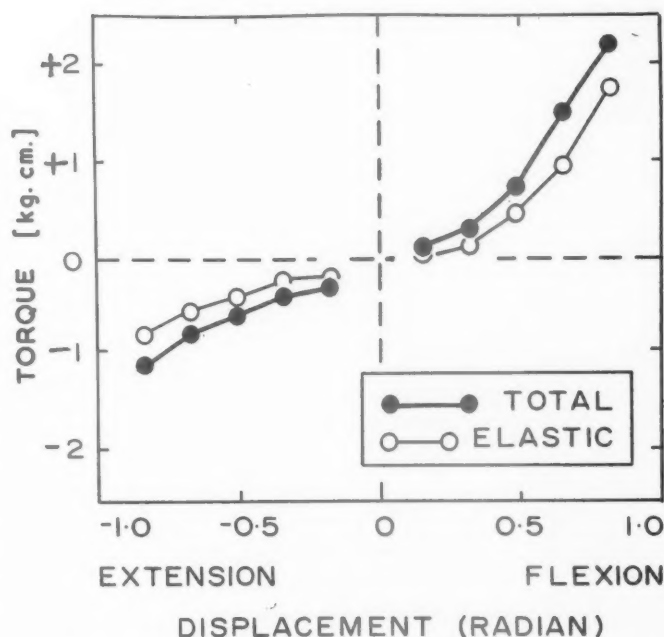


Fig. 6.—Relation of total and elastic stiffness to amplitude of rotation in a normal subject. There is a marked increase in stiffness at larger amplitudes of rotation. These data were obtained from studies illustrated in Fig. 7 (overleaf).

A tracing relating torque and rotational velocity is shown in Fig. 4. Viscous stiffness (gram-centimetres/radians per second) was determined by measuring the torque at maximum velocity. In sinusoidal motion, maximum velocity occurs at zero displacement, thus this torque was developed when the joint was in its mid position and was the torque required to overcome the sum of viscous stiffness and plastic stiffness.

Viscous stiffness was much smaller than elastic stiffness. The torque required to overcome total stiffness at maximum velocity was only one-tenth that needed to overcome elastic stiffness, and only a portion of this total stiffness was viscous stiffness.

In normal joints no torques attributable to friction could be demonstrated, even when a filter attenuating low frequencies was interposed in the torque measuring circuit. Such a filter permitted a 20-fold increase in amplification of torque by attenuating torques due to elasticity and viscosity whose fundamental frequencies were below 10 c.p.s.

A study of inertial stiffness independent of other types of stiffness was possible by substituting for the finger a cylinder of the same configuration and mass (27.2 g.). At accelerations below 56 radians per second² no torque due to inertial stiffness was measurable. Acceleration depends upon both frequency and amplitude of rotation. At maximum amplitude of rotation ($\pm 47^\circ$, or ± 0.833 radians) this acceleration is reached at a frequency of 1.3 c.p.s. At the usual amplitude ($\pm 29^\circ$, or ± 0.50 radians) a frequency of 1.7 c.p.s. is required to achieve an acceleration of 56 radians per second².

Stiffness was also studied under transient rather than cyclical conditions. That is to say, the joint

was displaced from the neutral position and held there, as opposed to the previously described methods in which the amplitude varied sinusoidally. Torque was recorded as a function of time on moving photographic film. Studies in all normal subjects revealed prominent stress relaxation (Fig. 7). Torque, or stress, waned with the passage of time. The final torque remaining after stress relaxation had run its course was solely attributable to elastic stiffness. The difference between the initial and final torque was due to viscous and plastic stiffness. Elastic stiffness accounted for upwards of one half the total stiffness at maximum amplitude (Fig. 6).

Physiological Variations

Sex.—31 men were paired with 31 women of the same age (within one year) and their stiffness compared. There was a highly significant difference between the stiffness in the men and in the women, the men showing greater stiffness (Table I).

TABLE I
COMPARISON OF STIFFNESS (kilogram-centimetres/radian) AT ± 0.44 RADIAN MAXIMUM ROTATION IN 31 MALES AND 31 FEMALES MATCHED TO WITHIN ± 1 YEAR OF AGE

Sex		Stiffness (kg.-cm./rad.)	
		At Flexion	At Extension
Male ..	Mean	2.31	2.96
	S.D.	0.81	1.30
	S.E.M.	0.15	0.24
Female ..	Mean	1.52	1.70
	S.D.	0.81	0.68
	S.E.M.	0.15	0.12
Difference ..		$P < 0.001$	$P < 0.001$

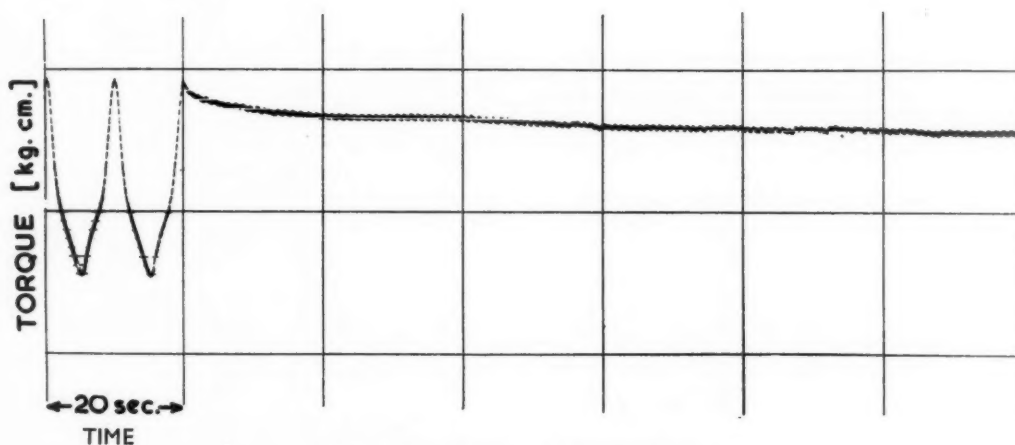


Fig. 7.—Stress relaxation in a normal subject.
Ordinate: Torque, 1.667 kg.-cm. per division.

After a displacement of 0.67 radians flexion the torque decreased from 1.55 to 1.00 kg.-cm. These data appear in Fig. 6.

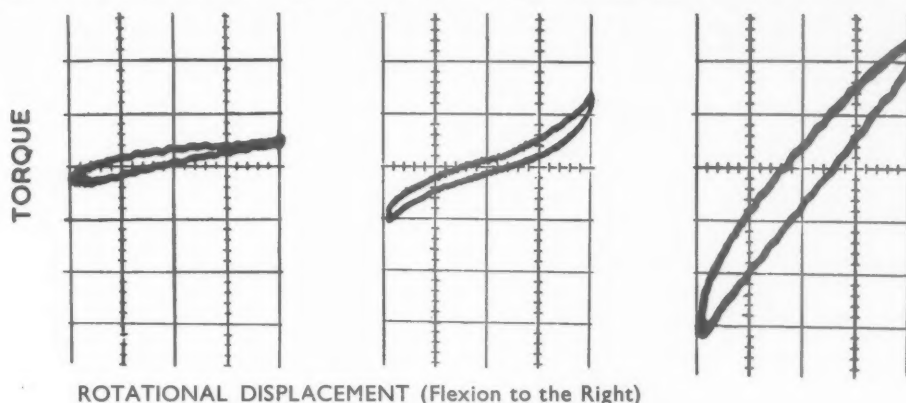


Fig. 8.—Effect of age on elastic stiffness.

Amplitude of rotation ± 0.44 radians.

Progressive increase in stiffness with increasing age is indicated by steepening slopes.

Age.—There were significant differences in stiffness with age. Records from three females aged 6, 28, and 66 years are shown in Fig. 8. There was progressive increase of stiffness with advancing age as indicated by the steeper slopes of the curves.

Temperature.—To determine the effect of cold, three experiments were done on two subjects, in which the hand was immersed in ice water until the skin temperature fell to 18°C . The temperature of the forearm muscles remained constant (recorded from an intramuscular thermistor needle). There was a 10 to 20 per cent. increase in stiffness on cooling.

To determine the effect of heat, the second metacarpophalangeal joints of two subjects were painted black and irradiated by an infra-red lamp to a surface temperature of 45°C . while the surrounding tissue was shielded by aluminium foil. Stiffness was measured at this temperature and at intervals as the temperature fell to normal. There was a 20 per cent. decrease in stiffness at 45°C . compared with the stiffness at 33°C . (Table II).

TABLE II

EFFECT OF INCREASING TEMPERATURE ON JOINT STIFFNESS (kilogram-centimetres/radian) IN TWO NORMAL SUBJECTS AT MAXIMUM EXTENSION

Amplitude of Rotation (rad.)	Subject 1			Subject 2		
	33.5°C .	45°C .	Percentage Decrease	33.5°C .	45°C .	Percentage Decrease
± 0.53	4.5	3.8	16	3.4	2.7	21
± 0.46	4.3	3.2	26	3.1	2.4	23
± 0.40	4.0	3.0	23	3.0	2.4	25
± 0.34	3.9	3.0	26	2.9	2.2	24

Effect of Oedema.—To investigate the influence of local oedema, saline was injected in the region of the joint capsule and the effect on joint stiffness was measured. Two control series of tracings were recorded; then 1 ml. was injected over the extensor aspect, followed by further 3 ml. in this region; then 4 ml. were injected over the flexor aspect. After each injection a series of tracings was photographed at low (0.1 c.p.s.), medium (1 c.p.s.) and high frequencies (1.3 c.p.s.) of rotation. After injection of 1 ml. into the extensor surface there was a 13 per cent. increase in stiffness on extension (Fig. 9).

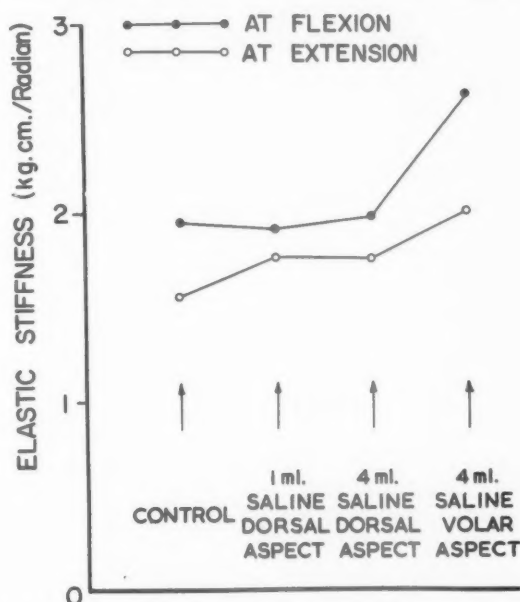


Fig. 9.—Effect of injecting saline subcutaneously around the joint. Saline injected into the extensor surface resulted in increased stiffness at extension, and that into the flexor surface produced increased stiffness at flexion.

The injection of a further 3 ml. produced no further increase in stiffness. The injection of 4 ml. into the flexor aspect produced a 33 per cent. increase in stiffness on flexion and a 9 per cent. increase on extension. The same relationship was present at all frequencies of rotation.

Connective Tissue Diseases

Increased Stiffness.—It was of interest that in arthritic joints the relation between elastic, viscous, and frictional stiffness was the same as in normal joints. Only in severely damaged joints which showed marked clinical and radiographic deterioration could friction be demonstrated (Fig. 10).

Even in these joints frictional stiffness did not contribute significantly to joint stiffness, the major component being increased elastic stiffness (Table III).

TABLE III

TORQUE (kilogram-centimetres) REQUIRED TO OVERCOME ELASTIC, VISCOUS, AND FRICTIONAL STIFFNESS IN A BADLY DAMAGED ARTHRITIC JOINT AND IN A NORMAL JOINT AT AN AMPLITUDE OF ± 0.53 RADIAN

Stiffness		Elastic	Viscous	Frictional
Joint	Arthritic ..	4.46	0.42	0.05
	Normal ..	2.90	0.29	0

Increased stiffness was sometimes observed in patients with inactive rheumatoid arthritis which had previously involved the metacarpophalangeal joints. This was illustrated by the results obtained in three women, one in the fifth decade, and two in the sixth decade. All three had definite rheumatoid

arthritis as defined by the criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959). There was no clinical evidence of activity and the erythrocyte sedimentation rates were normal. One had mild ulnar deviation at the metacarpophalangeal joints and another had a little residual swelling, but in none did the second metacarpophalangeal joint show any tenderness, pain, heat, redness, or limitation of movement within the range used in these experiments. All three, however, showed increased stiffness compared with groups of normal women of the same age.

Increased stiffness without active disease was also demonstrated in the joint of a man with chronic tophaceous gout. He was a 57-year-old white man who had had symptoms of gout for 15 years. At the time of testing he had tophi around the second metacarpophalangeal joint. Friction was demonstrated, but the force required to overcome it was very small compared with that required to overcome elastic stiffness, which proved to be the major component of his overall stiffness. Increased stiffness was also noted in a 42-year-old coloured woman with the chronic phase of the shoulder-hand syndrome.

Involvement of the second metacarpophalangeal joint by active rheumatoid disease increased elastic stiffness. Records were taken from a 42-year-old coloured woman with active rheumatoid arthritis of 5 months' duration whose arthritis subsided on treatment with prednisolone. They showed a marked decrease in stiffness following remission induced by prednisone, although it had not reverted to the normal pattern for a woman of this age.

Connective tissue diseases not involving the joint

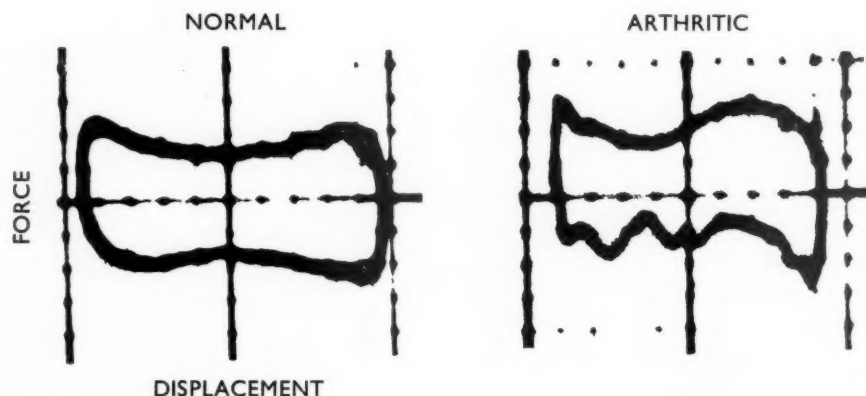


Fig. 10.—Demonstration of friction in a severely damaged joint.

Forces due to elasticity and viscosity have been attenuated to permit a 20-fold increase in the force scale (see text). The increased amplification fails to reveal irregular forces ascribable to friction in the normal joint, but these are readily apparent in the badly damaged joint.

directly caused increased joint stiffness subjectively and objectively. Two white women, both aged 39 years, who complained of stiffness of the hands, showed changes of systemic sclerosis on examination. The process was more advanced in one than in the other, but both showed elastic stiffness considerably greater than normal white women of their age (Table IV).

TABLE IV

STIFFNESS (kilogram-centimetres/radian) AT ± 0.47 RADIANS MAXIMUM ROTATION IN TWO PATIENTS WITH SYSTEMIC SCLEROSIS COMPARED WITH NORMAL WOMEN OF THE SAME AGE GROUP

Subjects		Stiffness (kg.-cm./rad.)	
		At Flexion	At Extension
Systemic Sclerosis	Woman (aged 39 years)	2.6	5.5*
	Woman (aged 39 years)	5.0*	11.0*
Normal	10 Women (aged 35-44 yrs)	Mean 1.72	1.76
	S.D.	0.84	0.46

* Significantly stiffer than in normal women.

Decreased Stiffness.—Decreased elasticity of the skin and hypermobility of the joints is found in certain hereditary connective tissue disorders. Two patients, a girl aged 16 years and a man aged 39 years, with Ehlers-Danlos syndrome showed decreased elastic stiffness at the joint. Further studies on the man revealed an increased rate of stress relaxation as measured by its half time.

These changes were less marked in patients with Marfan's syndrome. In the six patients studied the results were not significantly different from those in groups of normal subjects of comparable age.

Discussion

Joint stiffness has previously been measured by inexact methods, ranging from the subjective feeling of the patient (Cobb, Warren, Merchant, and Thompson, 1957) to the limitation of motion demonstrable by the observer (Ellis and Bundick, 1956; Williams, 1957). An extensive review of the literature has revealed that little has been done to measure joint stiffness with precision, either quantitatively or qualitatively (Wright and Johns, 1960b). We have described a method of assessing joint stiffness quantitatively in precise physical terms. Furthermore, the method characterizes the nature of the stiffness qualitatively by the physical terms elastic, viscous, frictional, inertial, and plastic

(Wright and Johns, 1960b). Reproducibility of results is good if care is taken in aligning the axes of rotation of the joint and the apparatus.

Although passive movements of tendons and muscles contribute to the stiffness measured at normal and diseased joints, it should be emphasized that no active contraction of muscle (voluntary or reflex) is found electromyographically. Moreover, the contribution of passive muscle and tendon movement does not obscure alterations in joint stiffness produced by physiological and pathological changes limited to the region of the joint (Wright and Johns, 1960a).

While active muscular contraction is not present in normal subjects, it may be of importance in the joint stiffness of certain neuromuscular disorders such as Parkinsonism and myotonia congenita. This type of stiffness is easily measured by these methods (Wright and Johns, 1960a). Thus, this technique measures objectively what the patient experiences subjectively in terms of stiffness at the joint whether due to arthritis or other disorders.

Voluntary muscular contractions occasionally occur during the course of an experiment. Such contractions produce distortions of the tracing which are readily apparent, and these records are disregarded.

Normal Subjects.—It is impossible to compare the various types of stiffness directly since they differ dimensionally. Direct comparison is possible, however, if one considers the force (torque) required to overcome the various types of stiffness at physiological speeds. In normal subjects the force required to overcome elastic and plastic stiffness is the most important, accounting for 90 per cent. of the total force required. Viscous stiffness ranks next in order of importance (9 per cent.), while inertial stiffness is negligible at the accelerations used. Indirect measurement has shown that, at the maximum acceleration used for the measurement of elastic stiffness in these experiments (17.3 radians per second²), the torque required to overcome inertial stiffness is one-hundredth of that needed to overcome elastic stiffness (Wright and Johns, 1960a). No friction is demonstrable in normal joints.

The joint, in common with other visco-elastic substances, exhibits non-linear elasticity. Increasing stiffness is observed with greater amplitudes of rotation. This may be due to the property (well exemplified in a rubber band) of the capsule becoming stiffer the further it is stretched. It may, however, be due to the fact that stiff elastic elements, such as ligaments and joint capsule, may be slack

until the extremes of joint motion are approached. The anatomy of the metacarpophalangeal joint with the tight apposition of tendons forming an integral part of the joint capsule suggests that the former explanation is probably the correct one.

Stress relaxation is easily demonstrable. With abrupt movements of the joint, the total force wanes with the passage of time due to stress relaxation. The reduction in force is more rapid at first, and becomes progressively slower. As infinite time is approached, only elastic force remains. Comparison of the initial with the final force indicates that under these circumstances elasticity contributes approximately half the total stiffness and plasticity together with some viscosity the remainder. Thus, the major single component in the stiffness of the normal joint is elasticity.

Physiological Variations.—There are marked differences in stiffness between the sexes, men being significantly stiffer than women. Since stiffness is expressed per joint, and since the joints of men are larger than those of women, joint size may in part explain this difference.

With advancing age differences in stiffness are apparent. The older the subjects, the more stiff they become. Again, joint size may contribute to the changes observed up to attainment of maturity. Size cannot explain increases in stiffness occurring after maturity. These increases may be related to changes in collagen of which the joint capsule is largely composed. It is well known that there is alteration of collagen with advancing age, shown by increase in fibril width (Gross, 1950), greater thermal contraction (Verzár, 1957), decreased susceptibility to collagenase (Keech, 1955; Tunbridge, 1957) and increased cross-linking (Verzár, 1957).

The effect of temperature changes localized to the joint is shown by increased stiffness at lower temperatures and decreased stiffness at higher temperatures. The latter effect probably accounts for the subjective benefit derived by arthritic patients from local heat such as paraffin-wax baths. The contention that a significant part of the stiffness measured at the joint is attributable to the joint itself is supported by these results. Here local temperature changes in the joint produce clear changes in stiffness while the temperature of more remote structures such as muscles remains constant.

The ability of changes localized to the region of the joint to produce changes in joint stiffness is further exemplified by the effect of the injection of saline in the region of the joint capsule. Elastic stiffness was increased by an injection of 1 to 4 ml. subcutaneously. The fact that saline injected into

the extensor aspect caused an increase in stiffness on extension rather than on flexion, and that saline injected into the flexor surface caused a greater increase in stiffness on flexion than on extension suggests that the effect is largely mechanical. These results illustrate the role that oedema may play in the stiffness of inflammatory arthritis. They also raise the possibility that oedema is responsible for the morning stiffness which is so characteristic a feature of rheumatoid arthritis, although other of our studies suggest that this is more likely to be a phenomenon of muscle weakness than of joint stiffness (Wright, 1959).

Connective Tissue Disorders.—It was surprising to find that in arthritic disorders elastic, viscous, and frictional stiffness maintain the same relative importance as in normal subjects. Even in the most badly-damaged joints the force required to overcome frictional stiffness accounts for only 1 per cent. of the overall stiffness. Similarly, although viscous stiffness is slightly increased, the force required to overcome it amounts to only 9 per cent. of the force required to overcome overall stiffness. It is of interest that not only patients with active rheumatoid arthritis but also some with inactive disease show increased elastic stiffness at the joint. This is probably due to residual changes in the joint capsule. The cause of the stiffness experienced by patients with degenerative joint disease is apparently due to changes in the joint capsule, whether primary or secondary, and not to damaged joint surfaces, for increased elastic stiffness is the major factor in this joint stiffness.

Involvement of tissue surrounding the joint capsule may influence joint stiffness. Thus it is probably involvement of skin and subcutaneous tissue in patients with systemic sclerosis which produces the marked increase in elastic stiffness. There was no radiological evidence of bone or joint involvement in our patients, although little is known about changes in the joint capsule in this disease.

Decreased elastic stiffness was noted in certain hereditary connective tissue disorders, such as Ehlers-Danlos syndrome and Marfan's syndrome. More detailed studies of the elastic stiffness and stress relaxation may yield information concerning the site of the basic lesion in these diseases, a subject about which there is remarkable confusion (Jansen, 1955; McKusick, 1959). Some of this confusion may have arisen from the clinical practice of first stating that the skin of patients with such disorders shows increased elasticity (Jansen, 1955; Zaidi, 1959) and then discussing the pathological lesion in terms of the physical causes of hyperelasticity.

In fact, in physical terms, the skin shows decreased elasticity (or elastic stiffness).

Summary

Using a method of measuring joint stiffness in precise physical terms, it has been shown that in normal and arthritic joints elastic stiffness is the major component in overall joint stiffness. There is significant plastic stiffness. Frictional and inertial stiffness are negligible, and viscous stiffness is small.

A study of 62 white subjects without arthritis showed a significantly increased elastic stiffness in men, and increasing stiffness with advancing age in all subjects.

Increased stiffness is produced by cooling the joint, by the injection of saline around the capsule, in patients with active rheumatoid arthritis and in some with inactive disease. Increased stiffness is also found in chronic tophaceous gout involving the joint and in systemic sclerosis.

Decreased stiffness follows the warming of the joint, and is also found in certain hereditary connective tissue disorders.

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Discussion.—DR. A. G. S. HILL (*Stoke Mandeville*) said that many rheumatoid patients were stiff in the evening when grip became weaker.

DR. WRIGHT agreed that he had found that in many subjects the power of grip diminished after 10 p.m. whether they went to bed or not.

PROF. S. J. HARTFALL (*Leeds*) asked what happened to grip and stiffness in rheumatoid patients on night work.

DR. WRIGHT said he had investigated one night worker, a hospital porter, who did not suffer from rheumatoid arthritis. He reversed his grip-rhythm and his temperature rhythm very rapidly. Since temperature rhythm usually takes 3 or 4 days to reverse, he wondered whether this man was an unusually labile subject as a result of being on shift work.

PROF. J. H. KELLGREN (*Manchester*) said that not all rheumatoid patients were stiff. There were also those with destroyed and excessively mobile joints. He asked whether they had made any observations on such patients, and which joint had been used for their measurements.

DR. WRIGHT replied that no observations had been made on that type of patient. The joint used had been the metacarpophalangeal joint.

DR. J. H. GLYN (*London*) asked whether there was any similarity between rheumatoid and athletic stiffness.

DR. WRIGHT replied that rheumatoid stiffness was probably not caused by changes in the muscles, whereas athletic stiffness was probably primarily muscular.

PROF. E. G. L. BYWATERS (*London*) asked whether any measurements had been made under anaesthesia.

DR. WRIGHT replied that he had not investigated patients during anaesthesia.

Analyse quantitative et qualitative de l'enraidissement articulaire chez des sujets normaux et chez les sujets atteints de maladies du tissu conjonctif

RÉSUMÉ

Grâce à un procédé permettant de mesurer l'enraidissement en termes physiques précis, on a pu démontrer que dans des articulations tant normales qu'arthritiques la rigidité élastique est le composant principal de l'enraidissement articulaire total. La rigidité plastique est significative. Les rigidités de friction et d'inertie sont négligeables et la rigidité visqueuse est minime.

Une étude de 62 sujets de race blanche non arthritiques a démontré une augmentation significative de l'enraidissement chez les hommes et une augmentation progressive chez tous les sujets au fur et à mesure que leur âge avançait.

L'augmentation de l'enraidissement par refroidissement de l'articulation (par injection péri capsulaire d'eau physiologique) survient chez des malades atteints d'arthrite rhumatismale évolutive et chez quelques sujets en période de rémission. L'augmentation de l'enraidissement apparaît aussi dans des cas de goutte tophacée chronique impliquant une articulation et aussi dans des cas de sclérose généralisée.

Une diminution de l'enraidissement survient après un réchauffement de l'articulation et aussi dans certaines affections héréditaires du tissu conjonctif.

**Análisis cuantitativo y cualitativo de la rigidez articular
en individuos normales y en pacientes con enfermedades
del tejido conectivo**

SUMARIO

Empleando un método que proporciona una medida en términos físicos precisos de la rigidez articular, se ha demostrado que en articulaciones tanto normales como artríticas la rigidez elástica es el componente principal de la rigidez articular total. La rigidez plástica es significativa. La rigidez de fricción y de inercia son negligibles y la rigidez de viscosidad es pequeña.

Un estudio de 62 individuos de raza blanca que no padecían artritis demostró un incremento significativo de la rigidez en los varones y aumento progresivo en todos los individuos a medida que la edad avanza.

Aumento de la rigidez por enfriamiento de la articulación (por inyección pericapsular de suero salino) se presenta en enfermos con artritis reumatoide evolutiva y en algunos en periodo de remisión. Aumento de la rigidez apareció también en casos de gota tofacea crónica afectando la articulación estudiada y en esclerosis generalizada.

Disminución de la rigidez aparece después del calentamiento de la articulación y también en determinadas afecciones hereditarias del tejido conectivo.

SPONTANEOUS ATLANTO-AXIAL DISLOCATION IN ANKYLOSING SPONDYLITIS AND RHEUMATOID ARTHRITIS

BY

J. SHARP AND D. W. PURSER

From the University Departments of Rheumatism Research and Orthopaedic Surgery, Manchester

Spontaneous atlanto-axial dislocation is a recognized if rare complication of infections of the pharynx and neck (Bell, 1830; Grisel, 1930; Watson-Jones, 1932) and of childhood rheumatic fever (Coutts, 1934). Werne (1957) reviewed the literature relating to the 176 cases reported up to that time in which the dislocation occurred in the course of various illnesses either without or with only trivial injury, and described seven further examples he had observed personally, five of them in children suffering from chronic polyarthritis. In this extensive literature, only isolated or small numbers of cases have been reported in which the lesion occurred as a complication of ankylosing spondylitis or rheumatoid arthritis.

Stammers and Frazer (1933) described a man aged 30 with advanced ankylosing spondylitis (Stammers, 1956) who developed pyramidal signs and sensory changes in the right lower limb and weakness of grip in the left hand as a result of forward dislocation of the atlas on the axis. The neurological abnormalities regressed after the head was extended and a plaster cast was applied. Rand (1944) reported a man probably suffering from ankylosing spondylitis in whom a Brown-Séquard syndrome was associated with atlanto-axial dislocation and Coste, Auquier, and Civatte (1952) described the case of a 37-year-old female said to be suffering from both ankylosing spondylitis and a primary chronic polyarthritis of 5 years' duration in whom atlanto-axial dislocation occurred without neurological complications. Kornblum, Clayton, and Nash (1952) reported two male patients with ankylosing spondylitis with severe forward displacement of the atlas; neurological complications were present in one case only and these disappeared after reduc-

tion of the dislocation by skull traction. Brocher (1955) gave brief clinical descriptions of two men with ankylosing spondylitis and atlanto-axial subluxation; in one this was spontaneous but in the other it is possible that displacement may have followed tonsillectomy. Morrison (1955) referred to a 31-year-old soldier suffering from severe and rapidly-progressing ankylosing spondylitis who developed a tetraparesis which was at first attributed to protrusion of a cervical disk but was subsequently found to be due to atlanto-axial dislocation (Morrison, Baird, and Logue, 1957). Wilkinson and Bywaters (1958) mention a patient with ankylosing spondylitis who complained of neck pain in whom radiographs disclosed atlanto-axial subluxation, and Pratt (1959) described two patients with severe ankylosing spondylitis who developed spontaneous atlanto-axial dislocations, one of whom was treated by occipito-cervical fusion.

Davis and Markley (1951) reported the clinical and autopsy findings in a 58-year-old female with severe nodular rheumatoid arthritis in whom the disease had resulted in severe destructive changes in the atlas, axis, and occiput with resulting dislocation of the atlas and compression of the medulla oblongata just below the pons by the odontoid process. The ganglion cells of the medulla showed pyknosis, eccentric nuclei, and vacuolization of the cytoplasm, but the brain and spinal cord were otherwise normal and there was no evidence of demyelination. Vignon and Patet (1955) described a 46-year-old woman who had developed an atlanto-axial displacement in association with rheumatoid arthritis of 8 years' duration. Storey (1958) reported the case of a 53-year-old woman with rheumatoid arthritis with a severe cord lesion who

died suddenly although wearing a protective collar; at autopsy the spinal cord was found to be compressed by the odontoid process which was displaced upwards through the foramen magnum from subluxation of the atlas on the axis. Pratt (1959) described the case of a 56-year-old woman with severe rheumatoid arthritis who developed tetraplegia as a result of atlanto-axial dislocation. Neurological improvement followed traction and the application of a cervical support, but she subsequently deteriorated, lost weight, developed melancholia, faecal and urinary incontinence, and decubitus ulceration, and died 7 months later.

In addition to these reports of the occurrence of atlanto-axial displacement in patients in whom rheumatoid arthritis began in adult life, this complication has also been observed in children with the disease (Potter, Barkin, and Stillman, 1954; Werne, 1957; Le Baudour and Freyberg, 1958) and also in a woman aged 31 in whom the arthritis had begun at age 10 and who had suffered from occipito-cervical pain from the age of 27 years (de Sèze, Djian, and Caroit, 1957).

In 1957 we reported ten patients with ankylosing spondylitis and two with rheumatoid arthritis who had developed spontaneous atlanto-axial displacements (Sharp and Purser, 1957). The purpose of the present communication is to report a further twelve patients with spondylitis and 24 with rheumatoid arthritis who have developed this complication, to point out that this is probably not a rare complication of advanced ankylosing spondylitis and is common in rheumatoid arthritis, and to describe the clinical features of the condition.

Radiological Criteria for Diagnosis

Coutts (1934) stated that an increase in the interval between the odontoid process and the anterior arch of the atlas was, in the absence of fracture of the odontoid process, the only pathognomonic radiological sign of atlanto-axial subluxation. From clinical observations, radiographic studies of himself, and published anatomical data, he concluded that normally the interval between the front of the dens and the back of the anterior arch of the atlas does not exceed 2 mm. Jackson (1950) examined lateral films of fifty adults taken in flexion and extension and found that the distance between the postero-inferior margin of the anterior arch of the atlas and the anterior surface of the dens did not alter and was never more than 2.5 mm. In eleven out of 25 children examined similarly, this interval increased in flexion to a maximum of 3 mm., the greatest increase observed in this series

being from 2 to 3 mm. In another child aged 6½ years who was referred to hospital 3 days after a head injury, the interval increased from 2.5 to 4.5 mm. on flexion. The child, who was symptomless, had no history of cervical infection and had a full range of cervical movement so that these measurements were presumably normal in his case. In studies of *post-mortem* preparations of the cervical spine, Werne (1957) found no forward slipping of the atlas on the axis on flexion until the transverse ligament retaining the odontoid process to the anterior arch of the atlas was divided; the dislocation then occurring tended to be greater in subjects below the age of 25. In flexion and extension films of 104 subjects aged from 10 to 62 years, either volunteers or patients suffering from trauma or local disease not involving the cranio-vertebral joints, he observed no forward movement of the atlas, although the cephalic end of the gap between the odontoid and anterior arch of the atlas usually became wider on flexion.

Prevalence Studies

All previous studies of the radiological criteria of normality had been made on hospital patients or normal volunteers, and it was felt that a more accurate definition of normality could be derived from studying radiographs of samples of the general population in which the prevalence of rheumatic disease had already been studied in detail (Kellgren and Lawrence, 1956, 1958; Lawrence, 1960).

General Population Sample.—The radiographs of the cervical spine of the population samples made available to us were single lateral films. It was appreciated that the absence of forward displacement of the atlas on a single lateral film taken in mid-position by no means excludes a mobile displacement which may be only apparent on a film taken in flexion (Fig. 1, opposite). The estimates of prevalence of atlanto-axial displacements in the general population derived from this study are therefore minimum values.

The number of films from the members of the general population examined was 1,478. Some 1,200 of these were from a random sample of the population over the age of 14 years in the Lancashire town of Leigh, and the remainder were from a random sample of females aged 55 to 64 years in the Vale of Glamorgan, from relatives of subjects with rheumatoid arthritis or multiple osteo-arthritis, and a small additional sample of people over the age of 75 in Leigh. In addition to radiographs of the cervical spine, x rays of the hands, feet, and in



Fig. 1.—(a) Conventional lateral view of a patient with rheumatoid arthritis; (b) Film taken in flexion of the same patient. The atlanto-axial subluxation is visible only on the film taken in flexion.

most cases other sites, had been taken in almost all of these individuals as well as a medical history, a clinical examination of the limbs and spine, and a sheep cell agglutination test (performed by the method of Ball, 1950).

The distribution of the distances between the middle of the anterior arch of the atlas and the

front of the odontoid process at various ages of the whole group is shown in Table I. The numbers with evidence of rheumatoid arthritis are also shown. Only four subjects with spondylitis, all males, were encountered in the population sample, and the interval measured 3 mm. or less in each case. It will be seen that six of the seven individuals over

TABLE I
MEASUREMENTS OF INTERVAL BETWEEN ODONTOID PROCESS AND ANTERIOR ARCH OF ATLAS ON RADIOGRAPHS OF TOTAL SAMPLE OF GENERAL POPULATION

Age (yrs)	Total Films	Total with Rheumatoid Arthritis*	Distance between Front of Odontoid and Back of Arch of Atlas (mm.)									
			3 or Less		3.1 to 3.5		3.6 to 4.0		4.1 to 4.5		> 4.5	
			Total	R.A.	Total	R.A.	Total	R.A.	Total	R.A.	Total	R.A.
15-24	72	1	69	1	2	0	1	0				
25-34	221	14	218	14	3	0						
35-44	227	17	226	17	1	0						
45-54	296	30	295	29							1	1
55-64	454	77	451	74	1	1	1	1			1	1
65-74	144	34	141	32	1	1			1	0	1	1
75 +	64	13	64	13								
Total	1,478	186	1,464	180	8	2	2	1	1	0	3	3

* The following criteria were taken as evidence of rheumatoid arthritis:

- (1) Definite clinical evidence, and/or
- (2) Definite radiological signs of the disease in the hands or feet, and/or
- (3) Agglutination at a titre greater than 1/16 in the sheep cell agglutination test (Ball, 1950).

the age of 45 in whom the interval was more than 3 mm. had evidence of rheumatoid arthritis; the exception was a man aged 72 who had suffered from osteomyelitis of the mandible between the ages of 8 and 16 and who might have developed a "hyperaemic" displacement during this period (Watson Jones, 1932). Films in flexion and extension were obtained in five of these seven individuals; in one the interval on the film taken in flexion was the same as that on the original film, in two it was slightly greater, and in two (including the subject whose original film is illustrated in Fig. 2), the distance could not be measured accurately for technical reasons but was greater than 3 mm. It therefore appears reasonable to regard a separation of the odontoid process from the anterior arch of the atlas of more than 3 mm. as abnormal after the age of 44, although a gap of 4 mm. may be normal in younger individuals and clinical evidence would strongly suggest that occasionally a gap of even 3 mm. after the age of 44 may be abnormal (Cases 14 and 17; Tables V and VII).



Fig. 2.—Radiograph of a man aged 59 in the random sample of the general population, showing well-marked forward displacement of the atlas. He had clinical evidence of severe rheumatoid arthritis and the sheep cell agglutination titre was 1/128.

The random sample of the general population contained an excess of individuals in the 55 to

64-year age group and the numbers with atlanto-axial displacements in the various decades after correction for this are shown in Table II. The incidence in the population aged 15 years and over was thus 2.6 per thousand (3/1,176) and in those over 55 years 8.5 per thousand (3/354). Each of the three individuals with an atlanto-axial displacement had clinical evidence of severe rheumatoid arthritis and a positive sheep cell agglutination test.

TABLE II
PREVALENCE OF ATLANTO-AXIAL DISPLACEMENTS ON RADIOGRAPHS OF A RANDOM SAMPLE OF THE GENERAL POPULATION

Age (yrs)	Number of Films	Number of Atlanto-Axial Displacements Found
15-24	74	0
25-34	221	0
35-44	228	0
45-54	299	0
55-64	197	2
65-74	111	1
75 +	46	0
Total	1,176	3

Table I shows that a total of 186 of the 1,478 members of the general population had clinical, radiological, or serological evidence of rheumatoid arthritis. Six of these 186 had atlanto-axial displacements, a prevalence of 32.3 per thousand. Five of these six had clinical evidence of rheumatoid arthritis, whereas 108 of the 186 had no clinical evidence of rheumatoid arthritis, 44 of them having radiological changes with or without a positive sheep cell test and 64 having only a positive sheep cell test without clinical or radiological evidence of the disease. Thus, of the 78 members of the general population who had clinical evidence of rheumatoid arthritis, five had atlanto-axial displacements, a prevalence of 64.1 per thousand. Kellgren and Lawrence (1956) have pointed out that approximately one half of the inflammatory polyarthritis occurring in middle-aged females in the general population and at present usually diagnosed as rheumatoid arthritis may be of a different nature, so that the prevalence of 64.1 per thousand is more accurately that in clinical "chronic inflammatory polyarthritis" as a whole rather than in clinical rheumatoid arthritis as such.

Hospital In-Patients with Rheumatoid Arthritis.—Lateral films with the cervical spine flexed and extended were taken as part of the routine radiological survey of almost all patients admitted to hospital under the care of the Rheumatism Service.

During 1958, 33 males and 46 females suffering from inflammatory polyarthritis of rheumatoid type were admitted, and of these 31 males and 43 females had such films taken (Table III). Atlanto-axial displacements were demonstrated in four males and ten females, giving a prevalence in the combined sexes of 189 per thousand of those with radiographs and 178 per thousand of the group as a whole, assuming that those without radiographs did not have displacements. None of these patients had been admitted to hospital purely on account of the atlanto-axial displacement and in most of them this was only diagnosed after admission. All of those with displacements showed positive results in the sheep cell agglutination test.

This estimate of the prevalence of atlanto-axial displacement in severe rheumatoid arthritis is lower than that deduced from *post-mortem* studies. In autopsies of twenty patients with rheumatoid arthritis, the majority of whom had very severe disease, Ball (1960) found atlanto-axial displacements in eight subjects.

TABLE III

PREVALENCE OF ATLANTO-AXIAL DISPLACEMENTS IN HOSPITAL IN-PATIENTS WITH RHEUMATOID ARTHRITIS, BY SEX

Sex	Male	Female	Total
No. of Patients	33 (31)	46 (38)	79 (69)
No. of Films	31 (30)	43 (35)	74 (65)
No. of Atlanto-Axial Displacements Found	4 (4)	10 (10)	14 (14)

Figures in brackets indicate the numbers giving agglutination at a titre greater than 1/16 in the sheep cell agglutination test.

Ankylosing Spondylitis.—Seventeen of the present cases were encountered in the examination and follow-up of patients referred to a Spondylitis Clinic where some 1,000 patients had attended. A survey of all the patients was not possible and it is likely that the diagnosis was missed in some patients who were seen before we became aware of this lesion as a complication of ankylosing spondylitis. That this is so is suggested by the finding of one previously undiagnosed case of atlanto-axial subluxation in the films of 49 spondylitic patients of various ages who were recalled to have flexion and extension films taken of the cervical spine. This cannot be regarded as the true prevalence since the sample is small and a completely random selection could not be made, but it is clear that the prevalence in ankylosing spondylitis is substantially lower than in rheumatoid arthritis.

The estimates of the prevalence of atlanto-axial displacement are summarized in Table IV.

TABLE IV

PREVALENCE OF ATLANTO-AXIAL DISPLACEMENT

Groups Examined		Prevalence per thousand
General Population	15 yrs and Over	2.6
	15 to 54 yrs	0
	55 yrs and Over	8.5
	With Any Evidence of Rheumatoid Arthritis	32
	With Clinical Evidence of Inflammatory Polyarthritis	64
Hospital In-patients with Rheumatoid Arthritis		189
Patients with Ankylosing Spondylitis		Not known but much less than in rheumatoid arthritis

Clinical Studies

The general features of the patients with ankylosing spondylitis and rheumatoid arthritis with atlanto-axial displacement are shown in Tables V and VI (overleaf). Details of the cervical displacement and its treatment are set out in Tables VII and VIII (overleaf).

All the patients with spondylitis had bilateral radiographic changes in the sacro-iliac joints, and in Cases 1 to 18 the clinical and radiographic picture was typical of ankylosing spondylitis. In Cases 19 to 22 the diagnosis was less straightforward. Case 20, in which there was a severe polyarthritis affecting the spine and limbs and a complete tetraplegia from the dislocation, is to be described in detail elsewhere (Sharp and Purser, 1961). Accounts of Cases 19, 21 and 22 are given in the Appendix to the present communication.

The eighteen patients with typical ankylosing spondylitis ranged in age from 28 to 64 years when the atlanto-axial displacement was diagnosed; seven were in the fourth decade but the ages of the remainder were fairly evenly distributed. Symptoms of ankylosing spondylitis had been present for from 3 to 31 years, for less than 10 years in nine patients and for more than 20 years in only four. In the seventeen patients in whom this could be ascertained, the cervical region had been involved for from 6 months to 22 years, in nine for 5 years or less, and in only two for more than 10 years. In Case 1 the first symptoms in the cervical region were indicative of atlanto-axial subluxation, but in the remainder these had supervened after cervical involvement had been present for from 9 months

TABLE V
 GENERAL FEATURES OF 22 SPONDYLITIS

Spondylitis	Case No.	Sex	Age at Diagnosis of Dislocation (yrs)	Duration to Diagnosis of Dislocation			Disease Activity at Presumptive Time of Dislocation	Spinal Deformity 0-3†	
				Symptoms of Spondylitis (yrs)	Cervical Symptoms (yrs)	Presumptive Dislocation to Diagnosis (mths)		Lumbo-Dorsal	Cervico-Occipital
Typical	1	M	35	8	1½	6	±	1	0
	2	M	31	3	3	26	+	2	1
	3	M	38	7	6	60	+	3	3 Flexion
	4	M	51	31	?	6	+	1	1
	5	M	38	19	8	30	+	1	3 Flexion
	6	M	28	5	5	3	0	1	3 Rotation
	7	M	37	14	9	36	+	2	2
	8	M	46	16	16	14	+	2	0
	9	M	54	9	4	2	+	2	3 Torticollis
	10	M	61	23	7	8	+	2	2
	11	M	57	22	22	24	+	1	+
	12	M	64	7	7	36	+	2	?
	13	M	29	6	4	18	+	1	1
	14	M	64	20	5	9	+	3	1
	15	M	32	5	5	?	+	2	0
	16	M	36	14	8	3	0	2	0
	17	F	55	25	5	12	+	1	2
	18	F	29	4	4	5	+	2	0
Atypical	19	M	18	20	0	"Some"	0	0	Forward inclination of head
	20	M	31	11	2	9	+	1	3 Flexion
	21	M	40	20	20	1½	0	1	2
	22	F	35	24	6	<12	+	1	+

† Graded from 0 = absent to 3 = severe.

to 20 years. The lumbar, dorsal, and lower cervical regions were rigid or grossly restricted in motion in fifteen patients, and ten had moderate or severe lumbo-dorsal flexion deformities. Atlanto-occipital movement, assessed clinically, was also greatly decreased in fourteen of the eighteen patients, seven of whom had moderate or severe occipito-cervical deformity from the displacement.

The patients listed in Table VI (Cases 23 to 48) all satisfied the criteria suggested in 1958 by the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) for a diagnosis of

Definite Rheumatoid Arthritis. All were adults of from 22 to 69 years of age, twelve being in the 6th, and six in the 7th decade. The majority were incapacitated by severe disease, and at the time the atlanto-axial displacement was diagnosed only five were capable of light employment or light household duties; eight were greatly restricted in activities and unemployed or unemployable, and thirteen were partially or completely bedridden. Subcutaneous nodules were present in fourteen, and eighteen of the 21 patients tested gave positive results in the sheep cell agglutination test (Ball, 1950). Symp-

TABLE V
FEATURES OF 22 SPONTANEOUSLY DISLOCATED PATIENTS

	Range of Spinal Movement at Diagnosis of Dislocation*				Main Presenting Symptom				Neurological Complications Present (0 to + + + +)
	"Atlanto-Occipital"	Cervical	Dorsal	Lumbar	Pain	Deformity	Neurological	Radiological	
0-3+	Full	$\frac{1}{2}$ -Full	0- $\frac{1}{2}$	0- $\frac{3}{4}$	+				0
1	$\frac{1}{4}$	Trace- $\frac{1}{2}$	0	$\frac{1}{2}$ - $\frac{1}{2}$	+				0
3 flexion	0	0	0	0		+			0
1	Trace	0-Trace	0	0	+				0
3 flexion	Trace	0	0	0	+				+++
3 rotation	Trace	Trace	0	0		+			++
2	Trace	0	0	0	+				0
0	Trace	0- $\frac{1}{2}$	0	0	+				0
3 torticollis	Full	Trace- $\frac{3}{4}$	0	0	+				++
2	Trace	0	0	0	+				+
+	Trace	0	0	0	+				±
?	Trace	0-?Trace	0	0			+		++++
1	$\frac{1}{2}$	0- $\frac{1}{2}$	0-Trace	0-Trace	+				0
1	"90"	Trace- $\frac{1}{2}$	Trace	Trace				+	0
0	Full	0- $\frac{1}{2}$	0	Trace- $\frac{1}{2}$	+				0
0	Trace	0-Trace	0	0	+				0
2	Trace	Trace	0	0	+				0
0	$\frac{1}{2}$ -Full	Trace- $\frac{1}{2}$	Trace- $\frac{1}{2}$	Trace- $\frac{1}{2}$	+				0
forward inclination head	0	0	Not Known		+				0
3 flexion	Full	0-Trace	0-Trace	0			+		++++
2	0	0-Trace	0	0-Trace	+				±
+	0	0	Not Known			+			+++

* Upper cervical extension and flexion were recorded as "atlanto-occipital" movement. In the lower cervical, dorsal, and lumbar regions, the ranges of flexion, extension, lateral flexion, and rotation were estimated. The minima and maxima in any of these ranges are recorded in Tables V and VI.

toms of rheumatoid arthritis had been present for 10 years or less in eleven patients and for more than 20 years in five, the range in the whole group being from 5 to 46 years. In Cases 31, 43, and 44 the disease had begun at or below the age of 15 years, in Cases 36 and 37 in the late teens but in adult life in the remainder. Symptoms of cervical involvement had been present for from 7 months to 13 years in the twenty patients who could date this with reasonable accuracy. In Case 31, a woman who was aged 30 when the displacement was diagnosed, in whom rheumatoid disease had begun at age 2, the

radiographic appearances in the cervical spine strongly suggested that this region had been affected in early childhood.

With the exception of Case 41, in which there was a severe lumbo-dorsal flexion deformity due to osteoporosis and osteomalacia secondary to a malabsorption syndrome, none of the rheumatoid patients had serious deformity of the lower spine but almost all of them had some restriction of dorso-lumbar movement, in most cases not severe. Cervical movement was also restricted in eighteen of the 22 patients in whom it was recorded, but to

Case No.	Sex	Subcutaneous Nodules	Sheep Cell Agglutination	Age at Diagnosis of Dislocation (yrs)	Duration to Diagnosis of Dislocation (yrs)			Disease Activity at Presumptive Time of Dislocation
					Symptoms of Rheumatoid Arthritis	Cervical Symptoms	Presumptive Dislocation to Diagnosis	
23	M	0	+	62	46	5	5	+
24	M	+	+	62	11	?	?	?
25	M	+	+	60	17	2	2	+
26	M	+	+	54	14	11	$\frac{1}{2}$	+
27	M	N.S.	N.A.	56	6	N.S.	$\frac{1}{2}$	+
28	M	0	+	52	6	6	2 wks	0
29	M	0	Neg.	55	8	8	1 $\frac{1}{2}$	+
30	M	+	+	61	7	7 mths	7 mths	+
31	F	0	Neg.	30	28	?28	>6	?
32	F	0	N.A.	32	10	9	?	?
33	F	0	+	68	8	4	>3	+
34	F	+	+	69	6	1	<1	+
35	F	+	N.A.	46	21	?	?	?
36	F	0	+	32	15	2	?	?
37	F	0	+	54	38	4 (?40)	2 $\frac{1}{2}$	+
38	F	0	Neg.	55	11	11	?	?
39	F	+	N.A.	61	8	N.S.	?	?
40	F	+	+	51	5	5	$\frac{3}{4}$	+
41	F	+	+	51	14	>2	?	?
42	F	+	+	56	22	12	?	?
43	F	+	+	31	16	11	3	+
44	F	+	+	22	9	?	?	?
45	F	+	+	44	12	12	>5	?
46	F	0	+	57	6	6	$\frac{1}{2}$	+
47	F	N.S.	+	51	15	3	$\frac{3}{4}$	+
48	F	+	N.A.	50	20	13	13	+

† Graded from 0 = absent to 3 = severe.

a much less degree than in most of the patients with ankylosing spondylitis. The range of "atlanto-occipital" movement was regarded as normal in most cases, and excessive, although painless, in Case 43 and probably so in Case 30. This contrasts with the findings in the spondylitic patients.

Clinical Features and Diagnosis of Atlanto-Axial Displacement

The clinical picture of severe atlanto-axial dislocation is characteristic and easily recognized. In

less severe degrees of displacement when the diagnosis is not so obvious, symptoms including those due to neurological changes may remain unexplained unless this complication of ankylosing spondylitis or rheumatoid arthritis is considered. After the atlanto-axial displacement had been recognized in the earlier patients in this series, it was found that a fairly uniform pattern of symptoms and signs indicating a displacement could often be elicited and as a result less severe degrees of displacement were recognized more frequently.

In some severe mobile displacements, when there

LE VI

ENTS WITH RHEUMATOID ARTHRITIS

Spinal Deformity 0-3†		Range of Spinal Movement at Diagnosis of Dislocation*				Main Presenting Symptom				Neurological Complications Present (0 to + + + +)
Lumbo-Dorsal	Occipito-Cervical	"Atlanto-Occipital"	Cervical	Dorsal	Lumbar	Pain	Deformity	Neurological	Radio-logical	
0	0	Full	$\frac{1}{2}$ -Full	$\frac{1}{2}$ - $\frac{3}{4}$	$\frac{1}{2}$ - $\frac{3}{4}$				+	0
0	0	Full	$\frac{3}{4}$ -Full	Trace-Full	$\frac{1}{2}$ -Full				+	±
1	0	Full	$\frac{1}{2}$ -Full	$\frac{1}{2}$	0- $\frac{1}{2}$	+				+
0	0	< $\frac{1}{2}$	$\frac{1}{2}$ - $\frac{3}{4}$	$\frac{1}{2}$ - $\frac{3}{4}$	$\frac{1}{2}$ - $\frac{3}{4}$	+				±
N.S.	N.S.	N.S.	N.S.	N.S.	N.S.			+		+ + + +
1	0	N.S.	N.S.	N.S.	N.S.	+				0
0	0	Full	$\frac{3}{4}$	$\frac{1}{2}$ - $\frac{3}{4}$	$\frac{1}{2}$ - $\frac{3}{4}$	+				0
1	1	"Hypermobility"		Limited				+		++
0	Short neck	$\frac{1}{2}$	$\frac{1}{2}$ - $\frac{3}{4}$	$\frac{3}{4}$ -Full	$\frac{3}{4}$ -Full				+	0
0	0	Full	$\frac{3}{4}$	Pregnant therefore not tested		+				0
1	1	Full	$\frac{1}{2}$ -Full	Limited	Good				+	0
1	0	Full	$\frac{1}{2}$ - $\frac{3}{4}$	$\frac{1}{2}$ - $\frac{3}{4}$	$\frac{1}{2}$				+	0
0	0	Full	$\frac{1}{2}$ -Full	$\frac{3}{4}$ -Full	$\frac{3}{4}$ -Full				+	0
1	0	Full	Full	$\frac{3}{4}$ -Full	$\frac{3}{4}$ -Full				+	0
0	0	Full	$\frac{1}{2}$ -Full	$\frac{1}{2}$ - $\frac{3}{4}$	$\frac{1}{2}$ - $\frac{3}{4}$	+				±
1	0	Full	Trace- $\frac{3}{4}$	$\frac{3}{4}$	$\frac{3}{4}$				+	0
N.S.	0	Limited	Very Limited	Good	Good	+				?
1	1	Full	Trace- $\frac{3}{4}$	Trace	Full	+				±
3	0	Full	Full	Very Limited	Limited				+	0
1	0	Very Limited	Very Limited	Limited	Limited				+	0
0	0	Increased	Full	$\frac{3}{4}$ -Full	$\frac{3}{4}$ -Full				+	0
1	0	Full	$\frac{1}{2}$ -Full	Full	Full				+	0
0	N.S.	N.S.	$\frac{1}{2}$ - $\frac{3}{4}$	N.S.	N.S.			+		++
1	0	Full	$\frac{1}{2}$ -Full	$\frac{1}{2}$ -Full	$\frac{1}{2}$ -Full				+	0
N.S.	N.S.	N.S.	N.S.	N.S.	N.S.			+		+ + + +
N.S.	N.S.	Very Limited		N.S.	N.S.			+		+ + + +

* Upper cervical extension and flexion were recorded as "atlanto-occipital" movement. In the lower cervical, dorsal, and lumbar regions, the ranges of flexion, extension, lateral flexion, and rotation were estimated. The minima and maxima in any of these ranges are recorded in Tables V and VI.

was little pain or muscle spasm, it was also found that the abnormal atlanto-axial mobility could be demonstrated clinically. The palm of one hand was placed on the patient's forehead and the thumb of the other on the tip of the spinous process of the axis. The patient was then asked to relax the neck in a semi-flexed position. By pressing backwards with the palm a sliding motion of the head backwards in relation to the spine of the axis could be demonstrated. The movement was usually only appreciated by the observer, but in one patient (Case 43) was also clearly visible.

In Tables V and VI the main presenting features of the cases are indicated and illustrative case histories are included in the following account of these modes of presentation.

Pain.—This was experienced in the upper cervical, suboccipital, and occipital regions, sometimes continuously and sometimes episodically. When the pain was very severe, its area of reference extended to the temporal or even frontal regions and to the back of the eye on one or both sides. It was usually aggravated by sudden movement of the

TABLE VII
RADIOGRAPHIC FEATURES AND TREATMENT OF 22 PATIENTS

Case No.	First Film				Diagnosis Film							Neurological Changes (0 to +++)
	Date	Depth Ant. Atlanto-Axial Joint (mm.)	Inclination (°)	Per cent. Width of Original Spinal Canal	Date	Depth Ant. Atlanto-Axial Joint (mm.)	Inclination		Mobility		Per cent. Width of Original Spinal Canal	
							Extension (°)	Flexion (°)	Traverse (mm.)	Angular (°)		
1	18.10.50	2	— 10	100	2.8.56	4	— 9	0	3	9	90	0
2	8.6.55	4	+ 3	90	8.5.57	8	+ 10	+ 12	0	2	75	0
3	—				20.9.55	12		+ 13	N.A.	N.A.	35	0
4	—				24.10.56	4	— 6	— 4	0	2	90	0
5	22.7.53	<2	— 8	100	15.9.55	16		+ 18	N.A.	N.A.	25	+++
6	—				7.6.57*	Not measurable						++
7	—				20.3.56	15		0	N.A.	N.A.	40	0
8	3.4.54	1	— 10	100	4.7.56	4	— 10	+ 6	2	16	90	0
9	—				20.7.56	7	— 8	+ 23	7	31	75	++
10	8.8.47	2	— 6	100	13.9.56	6	— 12	— 5	2	7	80	+
11	24.1.55	9	+ 3	70	30.5.56	10	— 5	+ 4	5	9	70	0
12	8.2.55	6	+ 27	55	26.10.55	10	+ 30	N.A.	N.A.	N.A.	30	++++
13	—				24.5.57*	2	— 32	— 12	1	20	100	0
14	17.10.56	1	— 15	100	13.12.56	3	— 16	0	2	16	90	0
15	—				12.11.58	9	— 6	+ 11	4	17	70	0
16	30.6.54	<1	— 17	100	22.1.59	5	— 12	— 5	2	7	90	0
17	26.3.57	3	+ 5	90	25.4.57	3	+ 15	+ 17	1	2	95	0
18	18.4.57	2.5	— 17	95	21.11.57	5.5	— 30	— 20	3	10	75	0
19	—				1945	Not known						0
20	21.9.53	3	— 15	95	26.11.54†	17	— 6	+ 21	5	27	25	++++
21	24.4.57	1.5	— 3	100	12.9.58	6	— 11	N.A.	N.A.	N.A.	70	±
22	—				1947	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	+++

* Rotary displacements.

† Post mortem films.

head or by the jarring of a bus or car ride. Some patients stated that such journeys were only possible if their heads were steadied by cradling their chins in their hands, or if they sat on side seats facing inwards. Pain of this character was greatly in-

creased in one patient (Case 17) after general anaesthesia, and in another (Case 8) by a course of active exercises aimed at increasing the range of movement of the head and neck. In four patients with ankylosing spondylitis the pain was not

TAB LE VII
ENT OF 22 PATIENTS WITH ANKYLOSING SPONDYLITIS

Neuro- logical Changes (0 to +++)	Treatment	Clinical Result	Last Film						Per cent. Width of Original Spinal Canal
			Date	Depth Ant. Atlanto- Axial Joint (mm.)	Inclination		Mobility		
					Extension (°)	Flexion (°)	Traverse (mm.)	Angular (°)	
0	None	Remission with aspirin	16.3.57	4	-10	0	3	10	95
0	Collar	Excellent relief	28.1.59	4	+ 4	+ 9	0	5	90
0	Skull traction. Occipito-cervical fusion	Complete relief	7.8.56	4	-25	-25	0	0	80
0	None. Defaulted	—	—						
+++	Traction. Fusion	Complete symptomatic relief and almost complete neurological recovery	6.10.56 4.6.59	6 6	-12	-12 -12	0	0	70 70
++	Traction. Plaster→Plastic collar	Symptoms relieved and almost complete neurological recovery	29.1.59	3.5	-21	N.A.	N.A.	N.A.	95
0	No symptoms when diagnosed. Collar during physical treatment	—	9.8.56	15	0	0	0	0	40
0	None	Intermittent pain	5.1.60	2	-12	- 7	2	5	100
++	Traction. Fusion	Mild residual pyramidal signs	23.10.56	5	-14	-14	0	0	80
+	Traction. Fusion	Complete regression of cord signs	24.4.57	4	-15	-15	0	0	80
0	Traction. Fusion	Complete relief	6.10.56	2	- 8	- 8	0	0	100
+++	Traction. Fusion	Minimal residual cervical pain and neurological changes	3.10.56	4	- 1	- 1	0	0	90
0	Traction. Plaster. Collar	Complete relief	30.3.60	1.5	-35	-17	0.5	18	100
0	Serial plasters. Collar	Recurrence of deformity but little pain after removal	10.4.58	3.5	-17	-10	2.5	7	85
0	Collar → Traction → Fusion. "Halo" from 5th to 12th wk	Complete relief	21.7.59	2.5	- 4	- 4	0	0	90
0	Collar	Complete relief	21.4.60	3.0	-21	- 4	2	17	95
0	Traction. Fusion	Complete relief	—						
0	Cardboard→Plastic collar	Pain relieved	25.2.60	7.0	-20	-17	0.5	3	70
0	Traction→Immobilization for 9 mths. Fusion, 1949	Recurrence of symptoms 18 mths after immobilization. Relief after fusion	24.4.57	19	0	0	0	0	30
+++	None	Tetraplegia. Death	—						
±	Traction. Fusion	Complete relief of pain and subsidence of neurological symptoms	22.9.58§	1.5	-21	N.A.	N.A.	N.A.	>90
+++	Traction. Laminectomy C.I. Fusion	Mild neurological residua	26.4.54	12	+20	N.A.	N.A.	N.A.	30‡

† Estimated. Partial operative removal of posterior arch of atlas.

§ On traction before fusion. Position unaltered on 30.12.58 after union of graft, but film not satisfactory for measurement.

relieved by radiotherapy. On the other hand correction and stabilization of the displacement resulted in complete relief of symptoms.

Case 8. Ankylosing Spondylitis.—A male crane-driver aged 44 years first attended in April, 1954, with

advanced ankylosing spondylitis of 14 years' duration. He had a total flexion deformity of 30° and his lumbar and dorsal spine was rigid. Although the lower cervical spine had greatly restricted movement there was a full range at the "atlanto-occipital" joint. Radiographs of the spine showed changes typical of ankylosing spondylitis

and the relations of the atlas to the axis were normal.

His main disability arose from a painful restriction of hip movement, and he was given radiotherapy to the hips with good relief of symptoms.

He next attended in September, 1955, having developed a severe pain in the neck 4 months previously. There was now only a trace of cervical movement. Radiotherapy on this occasion failed to relieve his symptoms and within one month he was complaining of much pain in the back of the head. During the next 5 months, whilst in hospital having physical treatment, his symptoms were intermittent and it was noted on discharge that there was increased mobility in the cervical spine. Although he became free from pain this recurred within a month of his leaving hospital and he found that his head seemed to slip forwards towards the end of the day. Radiographs revealed a 4-mm. separation of the odontoid from the anterior arch of the atlas on flexion of the neck, which decreased to 2 mm. on extension of the head. There was also considerable angular mobility of the atlas on the axis (Table VII).

He was warned of the possible dangers of violent head movements, particularly flexion, and was kept under observation as an out-patient, but was given no specific treatment for the displacement. He has continued to have episodes of severe upper cervical and occipital pain lasting weeks to months with intervening periods of several months of virtually complete freedom. When riding on buses he always chooses a side seat, since jogging movements of the head, particularly in an antero-posterior direction invariably aggravate and may precipitate the pain. Judged from the most recent radiographs taken 2½ years after the first diagnosis, the displacement has not increased in degree and the atlanto-axial mobility appears to be slowly decreasing (Table VII).

COMMENT.—The symptoms of atlanto-axial displacement in this patient were intermittent. In him and in three others, Cases 4, 5, and 11 (Table V), they were misinterpreted as evidence of reactivation of the spondylitis; in retrospect it is not surprising that radiotherapy failed to relieve them. An increase in movement of the neck and aggravation of the pain followed physical treatment; this case illustrates the possible dangers of intensive exercises in a patient with grossly restricted movement of the cervical spine.

Case 17. Ankylosing Spondylitis.—A housewife aged 55 years first had symptoms of ankylosing spondylitis at age 30. Over the years, as pain and stiffness spread up the spine, she developed an increasing flexion deformity. Her cervical spine was greatly restricted in motion from age 50. In spite of this progression her general health remained good and she led an active life with decreasing pain as her spine became more limited in motion. When she was 53 years old she first noted mild pains in her neck radiating up the back of her head to the vertex on jarring. About the same time she developed symptoms of peptic ulceration and later of pyloric stenosis for which after a year and a half she had a partial gastrectomy. Within

3 months symptoms returned and pyloroplasty was performed. Evidence of steatorrhoea was noted after the operations; her diet was generally deficient.

The upper cervical and occipital pain increased after the first operation and became even worse after the second; the pain was so severe when riding in vehicles that she supported her head with both hands. Her neck became almost rigid, the head being flexed on the neck. She was unable to restore her normal posture and any attempt to do so passively greatly increased the pain. Shortly after the second operation she developed paraesthesiae in the extremities, painful swelling of the feet and knees and, later, pitting oedema of the ankles. Examination at this time revealed an anaemic emaciated middle-aged woman in considerable distress. She stood with difficulty with an overall flexion deformity of 25°, due partly to the slight increase in dorsal kyphosis, but mainly to flexion of the head upon the neck. Her chin was rotated 10° to the right and there was slight downward tilting of the left side of the head. The spine was rigid apart from the upper cervical region where there was a trace of movement in all directions which caused severe occipital pain.

The liver and spleen were enlarged and there was evidence of a predominantly sensory peripheral neuropathy mainly affecting the lower limbs.

Radiographs (Table VII) revealed considerable (17°) forward tilting of the atlas upon the axis, but only 3 mm. separation of the odontoid from the anterior arch of the atlas in flexion, and these decreased to 15° and 2 mm. respectively on extension.

The pain was so intolerable that after her multiple nutritional deficiencies had been corrected skull traction was instituted and this was followed by immediate and almost complete relief of pain. Occipito-cervical fusion was performed with complete relief of cervical symptoms.

COMMENT.—This case illustrates the severe symptoms which may arise from minimal atlanto-axial displacement and the hazards to which such patients are exposed when under general anaesthesia.

Case 40. Rheumatoid Arthritis.—A housewife developed a generalized polyarthritis involving many limb joints and the cervical spine at age 46, and 3 years later, after two incomplete remissions, there was a deterioration in general health and joint condition so that she was reduced almost to a bed-chair life.

At the age of 51, 9 months before she was seen, when dozing in a chair she "nodded off" and as she did so felt a click in her neck. Her neck immediately became very painful and stiff, her head being flexed on the neck. This state of affairs continued for 6 months until, when she was reaching up to dislodge a fly, her head suddenly "slipped back" with relief of pain and return of movement. The neck had given no further trouble until one month before admission when, whilst being assisted in bed, she had fallen back on to the pillows with her husband's arm behind her neck. Again there was a click followed by sub-occipital pain which persisted and

was accompanied by a grinding sensation on moving the head, particularly into flexion.

On examination she was found to be anaemic and emaciated. She had severe destructive rheumatoid arthritis affecting almost all the limb joints with subcutaneous nodules over the elbows, lymphadenopathy, and splenomegaly. The plantar responses were equivocal, being difficult to interpret owing to the deformity of the feet; otherwise the nervous system appeared normal.

She had an almost fixed dorsal kyphosis of moderate severity and normal movement of the lumbar spine. She held her head slightly flexed on the neck. Movement of the head upon the neck was full but there was restriction of movement of the lower cervical spine. Movement was accompanied by pain in the neck and suboccipital regions and by audible crepitus.

Radiographs revealed a mobile forward subluxation of the atlas upon the axis with a 5-mm. separation of the dens from the anterior arch of the atlas in flexion. The third, fourth, and fifth vertebrae were each subluxated forwards.

She was provided with a padded cardboard collar and was started on steroid therapy. There was satisfactory relief of symptoms.

COMMENT.—This patient's course suggests that the atlanto-axial displacement followed the trivial event of "nodding off" in a chair, and illustrates the dangerous mechanical instability of the cervical spine commonly present in severe rheumatoid disease (Ball, 1958; Sharp, Purser, and Lawrence, 1958). In the management of

such patients we now assume that the cervical spine is excessively vulnerable to mechanical stress and take steps to protect them from this.

Occipito-Cervical Deformity.—In the patients with rheumatoid arthritis, deformity was not a prominent feature and was never the presenting manifestation. Sometimes the neck appeared foreshortened and the head carried forwards, but in general, and particularly in females when the occipito-cervical contour was obscured by the hair, the outward appearance was normal.

In ankylosing spondylitis, however, deformity was common. There were three components to this deformity. First, tilting forward of the atlas upon the axis fixed the head in some degree of flexion and as a result decreased an already diminished height of vision. Six patients complained of difficulty in shaving as a result of the chin being tucked into the neck. Many patients described a sensation of "falling forwards" of the head. Secondly, a forward displacement of the head flattened the normal contour of the occipital region (Fig. 3a, Case 7). Thirdly, some rotation and tilting of the head was usually present through asymmetrical slipping of the facets (Fig. 3b). In one man with a complete rotary dislocation of the atlas (Case 6), the head was fixed in full rotation to the right.

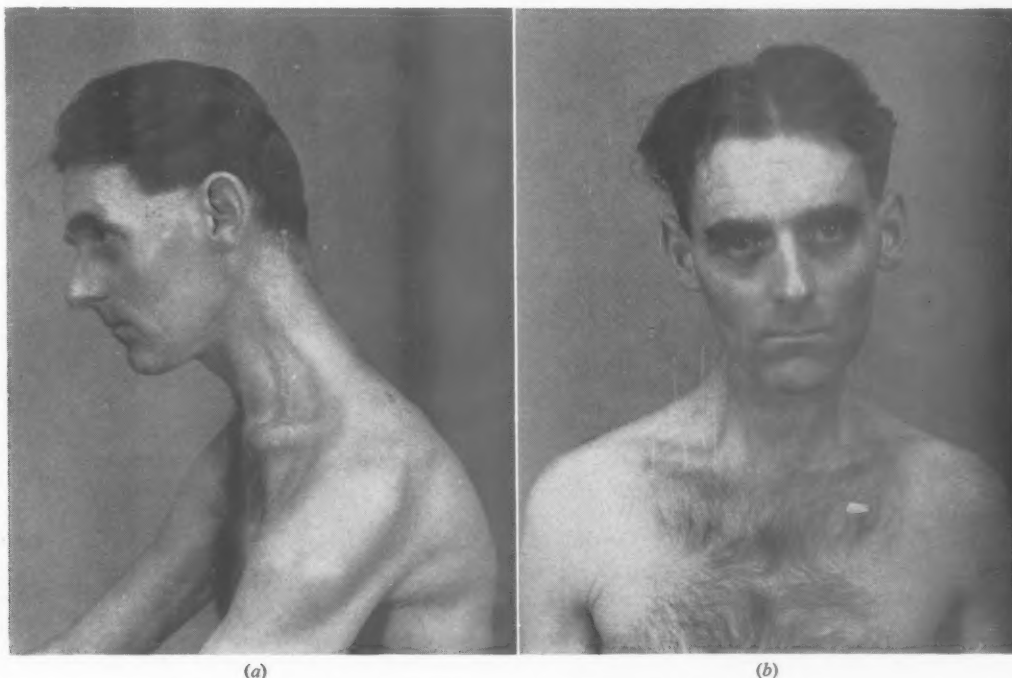


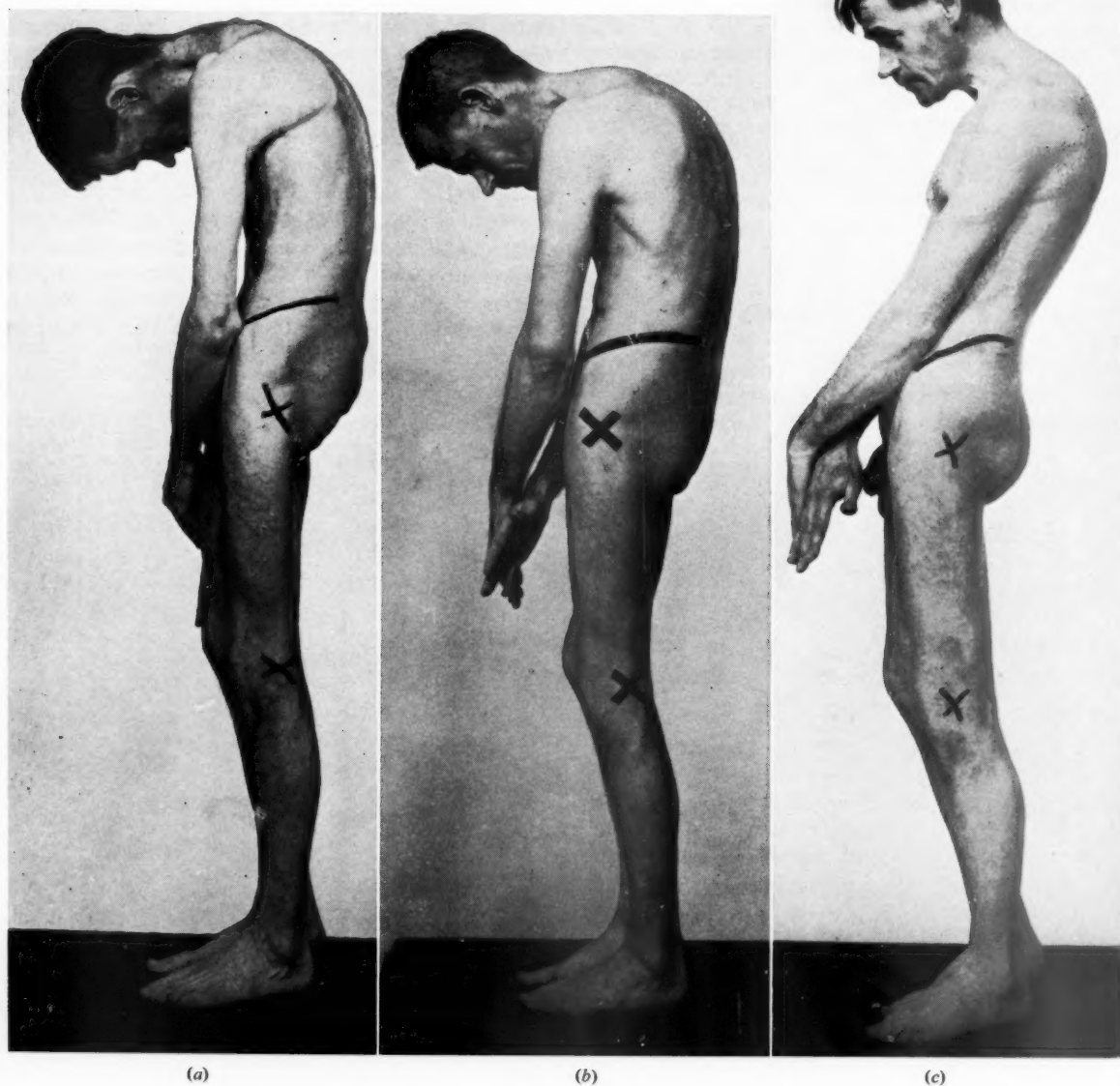
Fig. 3.—Case 7; the occipito-cervical curve is flattened and there is mild torticollis.

Case 3. Ankylosing Spondylitis.—A male cotton worker presented with severe ankylosing spondylitis at the age of 39 years. He had first noted low back pain when 32 years old. After some 12 months his general health deteriorated and he developed an increasing stoop and a rigid spine. Within a year his head began to "fall forwards" by degrees, with an associated almost constant dull frontal headache relieved by supporting his head with his hands. There was suboccipital pain on any attempted movement of the head. He noted increasing difficulty in shaving under his chin.

So extreme was his ultimate deformity that he was unable to open his mouth fully as his chin came in contact with his sternum and it was mainly on account

of his increasing difficulty in eating that his general practitioner referred him to hospital.

When he stood (Fig. 4a) his neck was at 10° below the horizontal. A minor degree of rotation of the head to the right and tilting to the left was also present. The whole spine was rigid and there was some limitation of movement of the hips. The chest expansion was reduced and there was evidence of bronchiectasis of the lower lobe of the right lung. The knee jerks were abnormally brisk, but there was no other neurological abnormality.



(a)

(b)

(c)

Fig. 4.—Case 3.

(a) Before treatment; (b) After occipito-cervical fusion; (c) After lumbar osteotomy.



Fig. 5.—Case 3.

(a) Before treatment, showing severe atlanto-axial dislocation; (b) After skull traction and occipito-cervical fusion.

Radiographs (Fig. 5a, Table VII) disclosed gross forward displacement and forward angulation of the atlas on the axis. The antero-posterior diameter of the spinal canal was reduced by about two-thirds. There was also a minor degree of fixed forward displacement of the seventh cervical on the first thoracic vertebrae.

Traction by skull calipers was instituted, and after 18 days the forward angulation of the atlas had been overcome and the distance between the dens and the anterior arch of the atlas had been reduced from 12 to 4 mm. 2 weeks later occipito-cervical fusion was performed. The patient's post-operative course was complicated by a sore on the forehead from the pressure of the plaster and by a brief flare-up of arthritis in the right hip joint. Although special attention was paid to the retention of mobility of the limb joints by supervised exercises, there was some decrease in the range of motion of both hips and the shoulders. Fusion occurred with the atlas in its corrected position (Fig. 5b).

In spite of maintaining good correction of the position of the head, the tip of the chin was still only 2 in. from the chest, and the face was still directed downwards when he was standing (Fig. 4b). Further correction of his posture was obtained by lumbar osteotomy, some 45° of extension being achieved at the level of the disk between the third and fourth lumbar vertebrae. 2 years after his first attendance he was free from pain and his function had been greatly improved (Fig. 4c).

COMMENT.—Reduction of the displacement and occipito-cervical fusion were indicated in this patient both on account of the disability due to the exceptionally severe deformity and also because of the danger of serious cord damage from trivial injury with an unstable atlanto-axial displacement of such magnitude.

Case 7. Ankylosing Spondylitis.—A 37-year-old industrial chemist first attended in March, 1956, suffering from advanced ankylosing spondylitis of 14 years' duration. His main disability arose from the hip joints which over the previous year had become very painful and grossly restricted in motion. He had a severe lumbo-dorsal flexion deformity, and his spine was almost painless but rigid apart from a trace of motion in the cervical region.

The attitude of his head (Fig. 3) strongly suggested atlanto-axial subluxation. His head was flexed and displaced forward on the neck with loss of the normal occipito-cervical curve, slight rotation of the jaw to the left, and downward tilting of the head to the right. Radiographs taken in attempted flexion and extension of the neck (Fig. 6, overleaf; Table VII) revealed that he had a stable atlanto-axial displacement; the only movements remaining were traces at the atlanto-occipital joints and between the second and third vertebrae.

The atlanto-axial displacement was causing no symptoms at this time and there were no neurological abnormalities, but inquiry revealed that for a period of about 2 months 3 years previously he had had severe lancinating pains from the upper cervical region to the vertex which had subsided without special treatment.

He was fitted with a block leather collar which he wore for some months whilst receiving physical therapy in hospital which, combined with x-ray therapy to the hips, resulted in some improvement. He then discarded the collar and since discharge from hospital has led an active life for 3 years with no symptoms from the subluxation.

COMMENT.—From the patient's history it appeared that the atlanto-axial displacement had become fixed spontaneously over a period of some 2 months. As

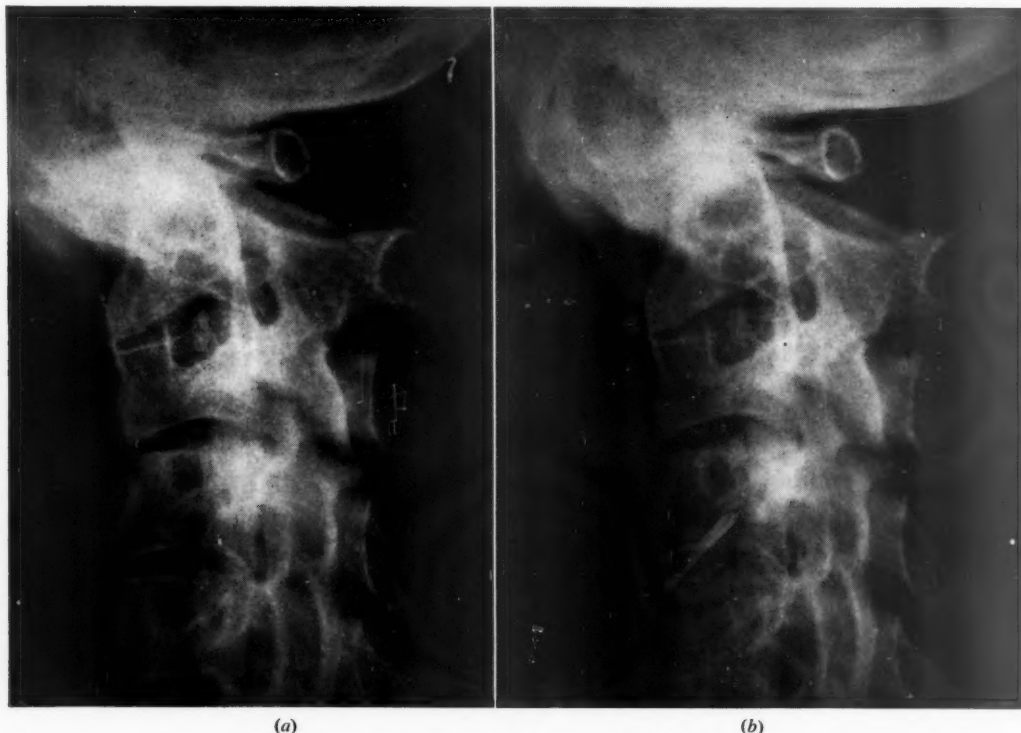


Fig. 6.—Case 7; radiographs: (a) in flexion, (b) in extension.

There is a trace of movement at the atlanto-occipital joints and of the 3rd on the 4th cervical vertebra; the atlanto-axial displacement is fixed.

the displacement was producing no symptoms and was stable and therefore appeared unlikely to produce cord damage, no treatment was thought to be indicated other than the use of a supporting collar in circumstances in which the neck was likely to be subjected to unusual mechanical stresses.

Presentation as an Unexplained Neurological Disorder.—Serious neurological complications from atlanto-axial displacements are probably rare in ankylosing spondylitis and rheumatoid arthritis, but in both conditions the presenting symptoms of the displacement may be those of disturbances of spinal cord function. The neurological syndromes produced may be bizarre and their cause obscure unless the possibility of atlanto-axial displacement is specifically considered. These neurological complications are to be dealt with in detail in a separate publication (Sharp and Purser, 1961), but the following case reports illustrate two of the more severe examples encountered in such patients.

Case 12. Ankylosing Spondylitis.—A 64-year-old male clerk attended hospital in January, 1955, complaining of painful stiffness of the neck of 7 years' duration. For 3 years his head had been sinking forward on to his chest. He was found to have advanced ankylosing spondylitis, with a rigid spine apart from a few degrees

of residual cervical movement. In addition to the changes of ankylosing spondylitis, the radiograph of the cervical spine (Fig. 7a, opposite) disclosed forward subluxation of the seventh cervical on the first thoracic vertebra, and subluxation of the atlas on the axis was in fact also present, although it was not observed at the time.

Over the next few months the patient found increasing difficulty in shaving under his chin because of a progressive forward sinking of his head, and he also noted occasional involuntary twitching of his back muscles. In October, 1955, over a few days he developed increasing weakness of the right hand and arm, involuntary twitchings of the right shoulder muscles, mild flexor spasms in the right leg, and disturbances of touch and temperature sensibility in the left hand. On three occasions when about to bend down he "collapsed like a rag doll".

When he was admitted to hospital the neurological signs suggested a partial transection of the upper cervical cord mainly on the right side. During the first few days in hospital the weakness of the right arm progressed to almost complete paralysis and he developed such great difficulty in coughing and breathing that he required treatment for a week in a Drinker respirator. Radiographs of the cervical spine now showed that, although the vertebral displacement was unaltered in the lower cervical spine, the atlas had slipped forwards a further 4 mm. (Table VII).

After an hour or so in the respirator in which his neck was in a position of maximum extension, there was

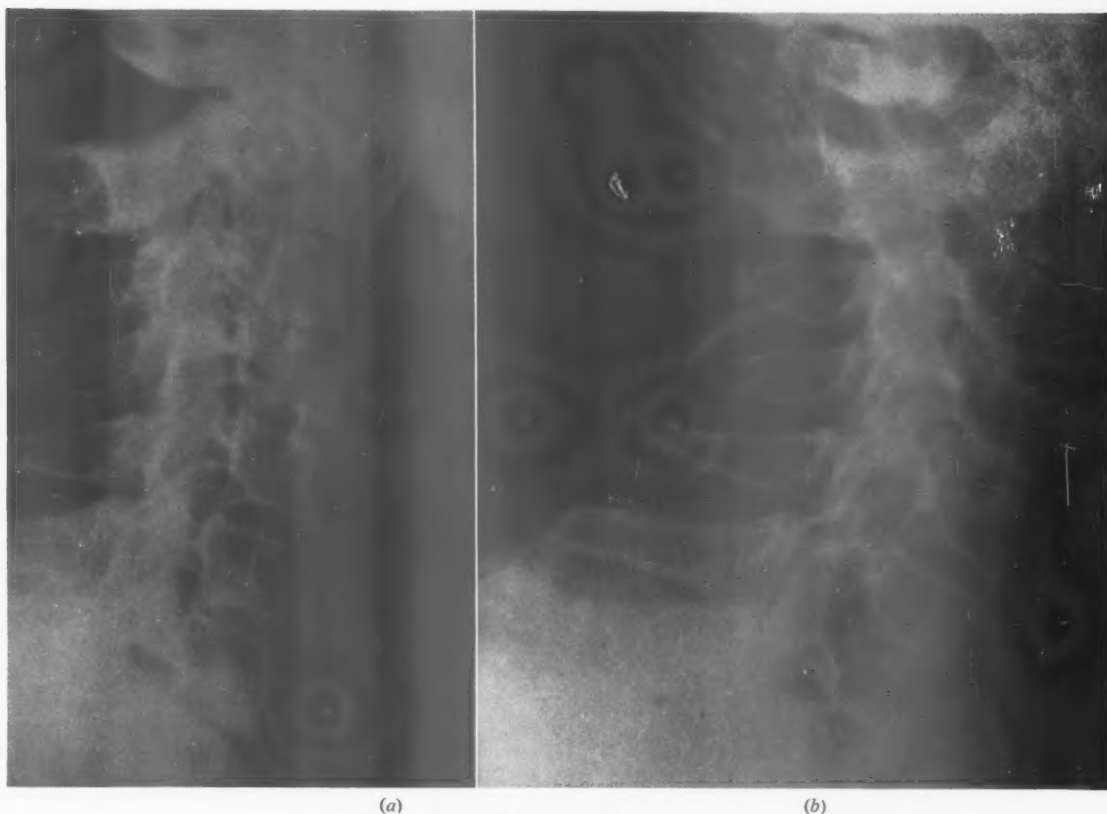


Fig. 7.—Case 12.

(a) Before treatment, showing forward displacement of the atlas on the axis and of the 7th cervical on the 1st thoracic vertebra; (b) After skull traction and occipito-cervical and cervico-dorsal fusion.

a distinct and sustained improvement in the neurological picture. Subsequently, after reduction of the displacements and fusion of both the upper cervical and cervico-dorsal region (Fig. 7b), his neck became virtually painless and there was an almost complete regression of the neurological signs.

COMMENT.—This case illustrates three points: first, the ease with which an atlanto-axial displacement may be missed in examining radiographs, particularly when other changes are present, notably a more obvious displacement lower in the neck; secondly, how, after a long period, severe neurological complications may rapidly supervene in a patient with an unstable displacement; and thirdly, the excellent recovery of neurological function commonly observed after reduction and stabilization of the displacement.

Case 47. Rheumatoid Arthritis.—A single woman aged 51 years developed severe progressive rheumatoid arthritis at age 35. Early in 1954 at age 48 she had experienced transitory episodes of pain in the neck and, after sitting with the head bent forwards as in sewing, aching in the sub-occipital region which would pass off 10 to 15 minutes after bringing her head up. The sub-

occipital pain steadily increased in severity, and shortly before Christmas, 1955, it radiated to the right temporal region. She now experienced a constant unpleasant sensation as if her head and neck were clasped in a vice, loss of temperature sensibility in the left foot, numbness and tingling in the left thigh and hand, and relief of the previously severe pain from her left hip. A few weeks later she developed precipitancy of micturition. In April, 1956, her right hand and arm became weak and position sense was lost. One month later the right leg became weak and heavy, but she was able to walk until an episode in which her left leg and arm "gave way". This occurred as she was making her way to an ambulance which was to convey her to hospital for a herniorrhaphy which fortunately passed without incident.

When admitted to hospital in July, 1956, she stated that she was sure that something had developed in addition to the arthritis "for I feel dreadful all over". Her state of general health was good. Apart from precipitancy of micturition and an inability to expel faeces from the rectum there were no visceral abnormalities. Severe destructive changes were present in almost all the joints and movement of the neck was painful, but the rheumatoid process appeared to be inactive and the erythrocyte sedimentation rate was only 5 mm./hr (Westergren).

Interpretation of the neurological changes was difficult on account of the joint disease. There was general muscle wasting and weakness maximal on the right side, with pyramidal signs including extensor plantar responses

in both lower limbs. Vibration sense was absent in the legs and sensibility to pin-prick and light touch as well as temperature discrimination were impaired or absent over the left leg and left half of the trunk up to the level

RADIOGRAPHIC FEATURES AND TREATMENT OF

Case No.	First Film				Diagnosis Film							Neuro-logical Changes (0 to + + + +)
	Date	Depth Ant. Atlanto-Axial Joint (mm.)	Inclination (°)	Per cent. Width of Original Spinal Canal	Date	Depth Ant. Atlanto-Axial Joint (mm.)	Inclination		Mobility		Per cent. Width of Original Spinal Canal	
							Extension (°)	Flexion (°)	Traverse (mm.)	Angular (°)		
23	—				25.6.57	8	— 4	+ 8	6	12	75	0
24	—				8.7.57	9	— 8	+16	9	24	65	±
25	—				5.4.57	4	— 7	0	3	7	85	+
26	—				20.5.57	6	—10	+ 3	5	13	80	±
27	—				13.1.56	13	— 7	+ 8	10	15	40	+ + + +
28	—				4.1.57	5	—20	—12	4	8	80	0
29	—				8.3.57	4	0	+ 8	2	8	80	0
30	—				20.10.58	15	—17	+ 2	11	19	35	++
31	10.12.51	4	— 9	75	20.5.57	4	—27	— 3	2	24	80	0
32	—				9.3.57	4	—13	— 8	3	5	90	0
33	18.6.54	4	— 6	80	1.5.57	9	—11	— 1	4	10	70	0
34	—				9.1.57	3.5	—15	— 7	3	8	85	0
35	—				15.4.57	6	—25	—14	5	11	80	0
36	—				12.3.57	4	—20	— 5	4	15	90	0
37	21.1.57	2→5	—3→0	85	11.6.57	6	— 4	0	4	4	80	±
38	—				7.5.57	4	— 7	0	2	7	90	0
39	—				24.5.57	4.5	+ 6	+ 6	1	0	80	?
40	—				24.9.56	5	—10	— 2	4.5	8	85	±
41	20.6.55	2	— 1	100	1.4.57	4	—15	— 8	3	7	95	0
42	—				29.2.57	6	—10	0	3	10	75	0
43	12.11.56	1	—20	100	21.7.57	13	—21	+12	12	33	35	0
44	—				30.1.57	4	—19	— 7	3	12	85	0
45	12.4.50	4	+ 5	80	20.6.55	8	+12	N.A.	N.A.	N.A.	50	++
46	—				7.2.57	4.5	—10	— 3	4	7	70	0
47	—				2.8.56	18	— 2	+ 4	10	6	35	+ + + +
48	—				21.2.57	8.5	0	N.A.	N.A.	N.A.	55	+ + + +

of the third thoracic segment. Position sense was impaired in the fingers of both hands. X rays (Fig. 8, overleaf; Table VIII) revealed gross atlanto-axial dislocation.

Skull traction by means of Crutchfield callipers

immediately relieved the pain in the neck and head and resulted in satisfactory reduction of the displacement. An occipito-cervical fusion was then performed. After this she was depressed, apathetic, hallucinated, and

TABLE VIII

26 PATIENTS WITH RHEUMATOID ARTHRITIS

Treatment	Clinical Result	Last Film						
		Date	Depth Ant. Atlanto-Axial Joint (mm.)	Inclination		Mobility		Per cent. Width of Original Spinal Canal
				Extension (°)	Flexion (°)	Traverse (mm.)	Angular (°)	
None	Continued symptom-free (December, 1957)	30.12.57	8	- 5	+10	6	15	70
Collar	Continuing symptom-free (November, 1959)	5.11.57	9	- 4	+15	9	19	65
Collar intermittently	Relief of pain and neurological symptoms and signs	4.3.59	5	-10	- 2	3.5	8	85
Collar	Pain incompletely controlled	3.2.59	7	-12	+ 5	5.5	17	80
Traction. Collar	Temporary improvement on traction. Deterioration in collar. Died October, 1956	—						
Collar	Complete relief of pain	17.7.59	2	-21	-12	2	9	90
Collar	Complete relief of pain	15.7.57	4	0	+ 3	1	3	85
Traction. Unsuccessful fusion	Death from septicaemia and multiple pyarthroses, September, 1959	11.9.59	13	-10	+ 3	2	13	35
None	No symptoms	26.8.57	5	-25	- 3	2	22	75
None	Patient defaulted							
Collar when sitting up	No symptoms							
None	No symptoms	13.7.57	4	-16	- 8	4	8	85
None	No symptoms	31.7.57	6	-23	-16	4	7	75
None	No symptoms	25.7.57	5	-21	- 6	5	15	85
Collar	Good relief of pain	25.5.59	6	- 2	+ 3	2	5	75
None	Minor neck stiffness only							
Collar	Died at home of a "seizure" 3 days after application	—						
Equivocal plantar responses. Collar. Steroids	Partial pain relief	—						
None	Continuing symptom-free (January, 1960)	—						
None	Also had staphylococcal septicaemia with metastatic infection of 7th cervical spinous process responding to antibiotics	8.7.57	8	-16	+ 2	6	18	65
Collar in vehicles, etc., when risk of violent neck flexion	No symptoms	6.5.59	12.5	-21	+10	11.5	31	40
Collar for a few weeks	No symptoms	25.2.59	3.5	-24	- 5	3.5	19	90
Traction. Fusion	Neurological improvement. Pain relieved	23.2.59	6	+ 2	+ 2	0	0	65
Collar	Good pain relief (maintained April, 1957)							
Traction. Fusion	Major neurological recovery	19.11.57	3.5	- 8	- 8	0	0	85
Traction. Fusion	Almost complete neurological recovery	2.10.58	8.5	+ 5	+ 5	0	0	55



Fig. 8.—Case 47; radiograph showing severe forward dislocation of the atlas on the axis.

disorientated as to time and place for some 10 weeks, but after her return to a normal mental state her progress was satisfactory. As she became more mobile the left knee from which deep pain sensibility was absent became more unstable, but she returned to a completely independent active life walking without sticks. When last seen 3 years after the operation she was very well, but still had a left lower quadrant loss of pain and temperature sensibility up to the level of the twelfth dorsal segment and minimal pyramidal signs.

COMMENT.—This patient had recognized the alteration in quality of her pain which had resulted from the disturbance of pain pathways in the spinal cord in addition to the other sensory disturbances. She was at serious risk at the time of the herniorrhaphy when she clearly had a severe unstable atlanto-axial dislocation.

Presentation as a Chance Radiological Finding.—In thirteen patients with rheumatoid arthritis the displacement was not suspected until radiographs of the cervical spine were examined. In none of them could a definite diagnosis have been made clinically, and detailed inquiry after the displacement had been diagnosed radiologically failed to elicit even a history of sub-occipital pain in six of them. This contrasts with the findings in the spondylitic patients, all of whom had symptoms of the displacement at some stage.

Case 33. Rheumatoid Arthritis.—A 60-year-old housewife first attended in 1949 with 6 months' history of painful swelling of the right knee. In 1950 the hands and feet became involved and in 1953 she developed severe rheumatoid changes in almost all the limb joints with mild restriction of spinal movement and some pain in the neck. In 1954 she was admitted to hospital and after rest in bed, intensive aspirin, and gold therapy, she had an excellent remission though with severe residual changes in the joints.

When the radiographs of hospital in-patients were reviewed for another purpose, an atlanto-axial subluxation was noted on a film of this patient taken in 1954 (Table VIII). On re-examination in 1957, apart from minor recrudescences, the remission of the arthritis had been maintained and she was leading a bed-chair existence with little pain. Her head was carried slightly forward but the deformity was hardly appreciable; neck flexion was full but movements in other directions particularly extension, although limited, were virtually painless. She could not recall ever having had any sub-occipital pain and there was no evidence of any neurological disturbance. Further radiographs indicated that the displacement had probably increased over the 3 intervening years (Table VIII). She was fitted with a supporting collar for use when sitting out of bed.

Duration of Symptoms of the Displacement before Diagnosis

An attempt was made by detailed questioning to determine when the patients had first developed symptoms indicating the atlanto-axial displacement. This was usually found to be easier in the spondylitic patients. In them the first symptoms of the displacement had occurred from 2 months to 5 years before it was diagnosed (Table V). In Case 7, where the displacement was fixed and was causing no symptoms at the time of diagnosis, these had been present for 2 months 3 years previously. In the remainder, symptoms of the displacement had been present constantly or intermittently from their appearance to the time of diagnosis. With three possible exceptions (Cases 1, 6, and 16 (Table V)), it appeared from the patients' histories that the disease process had been active at the time when the displacement had occurred.

In the seventeen rheumatoid patients in whom the duration of symptoms of the displacement could be ascertained with reasonable assurance, these had been present for from 2 weeks to 13 years, nine patients having had them for more than 1 year and four for 5 years or more. Since six of the thirteen patients in whom the displacement was first noted on radiographs had had no symptoms to indicate its presence, the displacement could also have been present for varying periods before the symptoms developed in the other patients.

Radiological Features

The radiological features of the patients with ankylosing spondylitis are indicated in Table VII, and of those with rheumatoid arthritis in Table VIII. The measurements recorded in these Tables which are illustrated in Fig. 9 were derived as follows:

- (1) The depth of the anterior atlanto-axial joint was taken as the distance between the middle of the posterior surface of the anterior arch of the atlas and the anterior surface of the odontoid process. Measurements were made using dividers on the film taken in flexion when available.
- (2) The inclination of the atlas to the axis was taken as the angle between the line joining the inferior borders of the anterior and posterior arches of the atlas and that joining the inferior border of the body of the axis and of its spinous process. A negative angle of inclination was recorded when the lines converged posteriorly and a positive angle when they converged anteriorly.
- (3) The "traverse" of the atlas on the axis represented the increase in depth of the anterior atlanto-axial joint in flexion, and the angular mobility was derived from the algebraic difference between the angle of inclination of the atlas to the axis in flexion and that in extension.
- (4) The antero-posterior diameter of the spinal canal on the film taken in flexion was measured as the shortest distance between the anterior surface of the posterior arch of the atlas and the posterior surface of the odontoid process. This was expressed as a percentage of that of the estimated original spinal canal of that individual to the nearest 5 per cent. The original size of the spinal canal was estimated by subtracting the antero-posterior diameter of the odontoid process plus an arbitrary 1 mm. for the original depth of the atlanto-axial joint from the distance between the anterior surface of the posterior arch and the posterior surface of the anterior arch of the atlas. Using the symbols for these measurements as in Fig. 9, the calculation is represented by the formula:

$$\frac{c}{D - (B + 1)} \times 100$$

As can be seen from Tables VII and VIII, the main determinant of the degree of narrowing of the spinal canal was the increase in depth of the anterior atlanto-axial joint, but extreme degrees of inclination of the atlas, either forwards or backwards, further increased the narrowing of the canal. Thus, in Cases 11 and 12 (Table VII), the depth of the anterior atlanto-axial joint was 10 mm. in each case but extreme forward tilting of the atlas in Case 12 had resulted in narrowing of the canal to 30 per cent. of the original compared with 70 per cent.

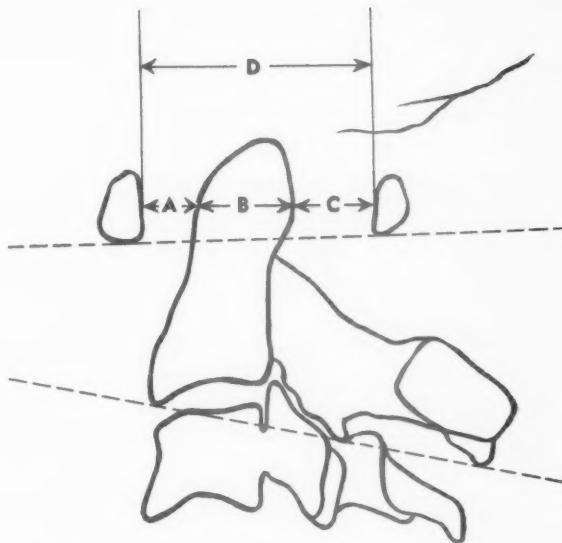


Fig. 9.—Diagram to illustrate measurements recorded in Tables VII and VIII.

in Case 11 in whom the forward tilting was much less. In Case 18, hyperextension at the atlanto-axial level slightly aggravated the narrowing of the canal consequent on the forward displacement of the atlas.

Two further changes were observed in the rheumatoid but not in these spondylitic patients. In a few, destructive changes in the lateral articular processes of the atlas and axis had resulted in a downward displacement of the atlas relative to the odontoid process which commonly broadens out inferiorly so that this tended to increase the narrowing of the canal. More often, there was erosion of the odontoid process, and when this affected the posterior and apical aspects this tended to decrease the narrowing of the spinal canal resulting from a given degree of anterior displacement of the atlas.

As might be expected, the most serious neurological lesions were observed in both conditions in patients with the greatest narrowing of the spinal canal. Thus, three of the five spondylitics and four of the five rheumatoid patients in whom the spinal canal was known to be narrowed to 50 per cent. of the normal or less had neurological changes of some severity. In one of the two exceptions among those with spondylitis, Case 7, the displacement was fixed radiologically on films taken 4½ months after diagnosis. In the other, Case 3, films in flexion and extension were not taken, but clinically the spine was rigid. The rheumatoid patient was a 31-year-old female (Case 43) who had an exceptionally mobile displacement with narrowing of the

canal to 35 per cent. of normal in flexion but who had no symptoms of the displacement and no neurological abnormalities.

Among the remaining spondylitic patients, Case 9, in whom the canal was narrowed to 75 per cent., and Case 10, with narrowing to 80 per cent., had moderately severe and mild cord damage respectively, and in Case 21 in which the evidence of mild cord damage was not conclusive the canal was narrowed to 70 per cent. of normal. In Case 6, which showed a rotary dislocation with moderate cord damage, the degree of narrowing of the canal could not be measured, and in Case 22, with evidence of fairly severe cord damage, the films taken before operation were not available.

In the rheumatoid patients the spinal canal in Case 48, in which there was a very severe cord lesion, was narrowed to 55 per cent. of normal in the conventional lateral view, but films in flexion were not taken. In Case 25, where the canal was 85 per cent. of normal, there were mild neurological changes, and in Case 24 and Cases 26, 37, and 40 there was equivocal evidence of cord damage with canals of 65 per cent. and of 80 to 85 per cent. of normal respectively.

In five of the thirteen patients with neurological changes (Cases 5, 6, 12, 22, and 48, including some with the most severe neurological lesions), films were not taken in flexion and extension so that the degree of abnormal mobility present could not be measured and the importance of this as a factor in the production of cord damage could not be assessed from this study. Although the findings in Case 43 provide a striking exception, we suspect that as a rule severe abnormal mobility may be an important contributory cause of cord damage.

Progress of Patients in Relation to Treatment

(1) Before Diagnosis

The radiological findings in the thirteen spondylitic and six rheumatoid patients in whom radiographs of the cervical spine taken at some time before the diagnosis of the displacement were available are indicated in Tables VII and VIII respectively. The findings in the earliest available films were recorded and with the exception of Case 37, who had had films in flexion and extension, the remainder had only conventional single lateral films.

In three of the spondylitic patients (Cases 2, 11, and 12; Table VII), a forward subluxation of the atlas was visible on the earlier film, and in each case the displacement was more marked on the films

taken at the time of diagnosis. Since, however, the presence or full degree of displacement may be apparent only on films taken with the neck fully flexed (Fig. 1), it cannot be concluded that the displacements had increased in the interval, or that they were necessarily absent in those in whom the appearances on the earlier conventional single lateral films were normal. In Case 16 radiographs in flexion and extension taken 2 years before diagnosis, at which time the patient had symptoms strongly suggesting a mobile atlanto-axial displacement, had revealed no evidence of this. The symptoms subsided spontaneously but recurred in more severe form in November, 1958, 3 months before the films revealing the displacement were taken.

An atlanto-axial displacement was visible on the earlier films of four of the six rheumatoid patients in whom these were available, Cases 31, 33, 37, and 45. Only in Case 31 had the displacement not apparently progressed at the time of diagnosis.

(2) After Diagnosis

(a) *Without Treatment.*—Four of the spondylitic patients were given no specific treatment for the displacement (Cases 1, 4, 8, and 20; Table VII). Case 4 was lost to follow up. In Case 1 the pain was relieved by aspirin and the displacement had not appreciably altered on radiographs taken 7 months later. In Case 8 intermittent episodes of pain from the displacement continued over 3½ years, but during this interval the displacement became reduced and the atlanto-axial mobility greatly diminished. In Case 20 the diagnosis was made only at autopsy; during the 9 months before death the patient had developed a progressive and ultimately complete tetraplegia and his death from debility and secondary infection was directly attributable to the atlanto-axial dislocation.

In seven of the nine rheumatoid patients given no specific treatment (Cases 23, 31, 32, 34, 35, 36, and 41; Table VIII), the displacement was producing no symptoms, and in Case 38 it was causing only minor pain. In Case 42 the wearing of a collar was made impossible by an infection of the seventh cervical spinous process as one of numerous sites of metastatic infection from staphylococcal septicaemia: the neck symptoms subsided with control of the infection. None of them had neurological changes. In each of the six patients who had further radiographs 3 to 6 months after diagnosis, there had apparently been further slight narrowing of the canal but with the exception of Case 42 the individual differences were probably within the error of measurement, and in Case 42 restriction of

neck movement due to pain from the bone infection may have prevented demonstration of the full range of abnormal mobility on the original films. Those initially without symptoms continued so throughout periods of observation of up to 2½ years.

(b) *Treatment by External Support.*—To achieve virtually complete immobilization of the upper cervical spine by external means in an ambulant patient, fixation to the skull either by incorporation of skull callipers in a Minerva plaster or by a device such as the "halo brace" (Perry and Nickel, 1959) is required. The conventional Minerva plaster does not immobilize the upper cervical spine (Fig. 10) and may not maintain reduction of an unstable atlanto-axial displacement.

In Case 27 there was an almost complete tetraplegia at the time when severe atlanto-axial dislocation was diagnosed. Good reduction of the displacement was achieved by skull traction, the antero-posterior diameter of the spinal canal returning to 95 per cent. of normal. The reduction was maintained in the first of two Minerva plasters which held the cervical spine in extreme extension, but radiographs in a second plaster applied 3 weeks later with the head in a more normal position revealed that the displacement had increased, the

canal now being only 75 per cent. of the normal diameter (Fig. 11a, overleaf). On films taken 4 weeks later in the same plaster the atlas had slipped further forwards so that the canal was now narrowed to 50 per cent. of normal (Fig. 11b, overleaf). From the time of institution of traction there had been steady and substantial neurological improvement and this continued up to the application of the second plaster. Thereafter, the patients' neurological status and functional capacity steadily deteriorated. After 3 months, the second plaster was replaced by a block leather collar, but the deterioration continued and after one month in the collar he was allowed to return home at his own request. He died 4 months later but we have been unable to obtain any further information about him.

Any form of supporting collar which allows the patient to speak and chew must also permit some upper cervical movement. Patients were therefore provided with supporting collars with the objects of restricting cervical movement, relieving pain, and affording some mechanical protection from violent head movements, notably flexion, and for the not unimportant reason that the collars also served to remind those looking after them of the presence of the lesion. Most of the patients were given a simple padded cardboard collar, but in a few instances more durable collars made of plastic material padded with foam rubber or of moulded block leather were provided and, as described below, one spondylitic patient was treated by serial plaster collars. The collars were well tolerated by the spondylitic patients, but greater care was necessary in those with severe rheumatoid arthritis to prevent pressure necrosis of the skin.

Four spondylitic patients were given cardboard or plastic collars as the only local treatment (Cases 2, 7, 16, and 18: Table VII). In Case 7, a stable displacement causing no symptoms was treated by a collar worn only while the patient was in hospital undergoing vigorous physical treatment. In the others pain from the displacement was completely relieved. In Case 2 partial and in Case 16 almost complete reduction of displacement occurred over periods of 20 and 15 months respectively. In Case 18 the displacement increased, but the abnormal mobility greatly diminished during 27 months of observation. Case 15 was at first treated with a cardboard collar and later with a plastic collar by day and cardboard one at night. Initially, his pain was satisfactorily relieved but it then recurred and after 4 months was more severe than at the outset. By this time there had been a very

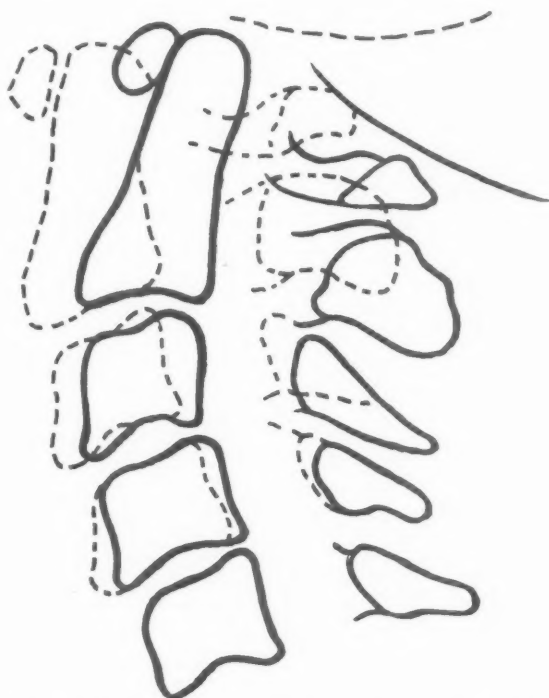


Fig. 10.—Tracings of radiographs of the cervical spine of a patient in a Minerva plaster, showing range of movement permitted.

slight increase in the forward displacement of the atlas, which was tilted forwards on the axis and almost fixed in the position of maximum deformity with further slight narrowing of the canal to 65 per cent. of normal. Reduction of the displacement by skull traction followed by occipito-cervical fusion completely relieved his pain and restored the canal to 90 per cent. of the normal diameter.

Case 14, an elderly Chinese male, who had a mild atlanto-axial displacement associated with a very severe lumbo-dorsal flexion deformity, was treated by periods of recumbency and serial plaster collars

with considerable but only temporary decrease in the deformity, but little if any effect on the displacement. One year after treatment there had been a minimal increase in the forward displacement of the atlas, but the angular mobility had diminished. He was suffering little pain and declined further treatment.

Of the rheumatoid patients, twelve were treated by supporting collars. Case 39 (Table VIII), who had a relatively mild and almost fixed displacement, died at home 10 hours after a "seizure" which occurred 3 days after the displacement had been diagnosed and she had been fitted with a padded cardboard collar; no further details could be obtained. The remainder wore collars continuously or intermittently for periods ranging from a few

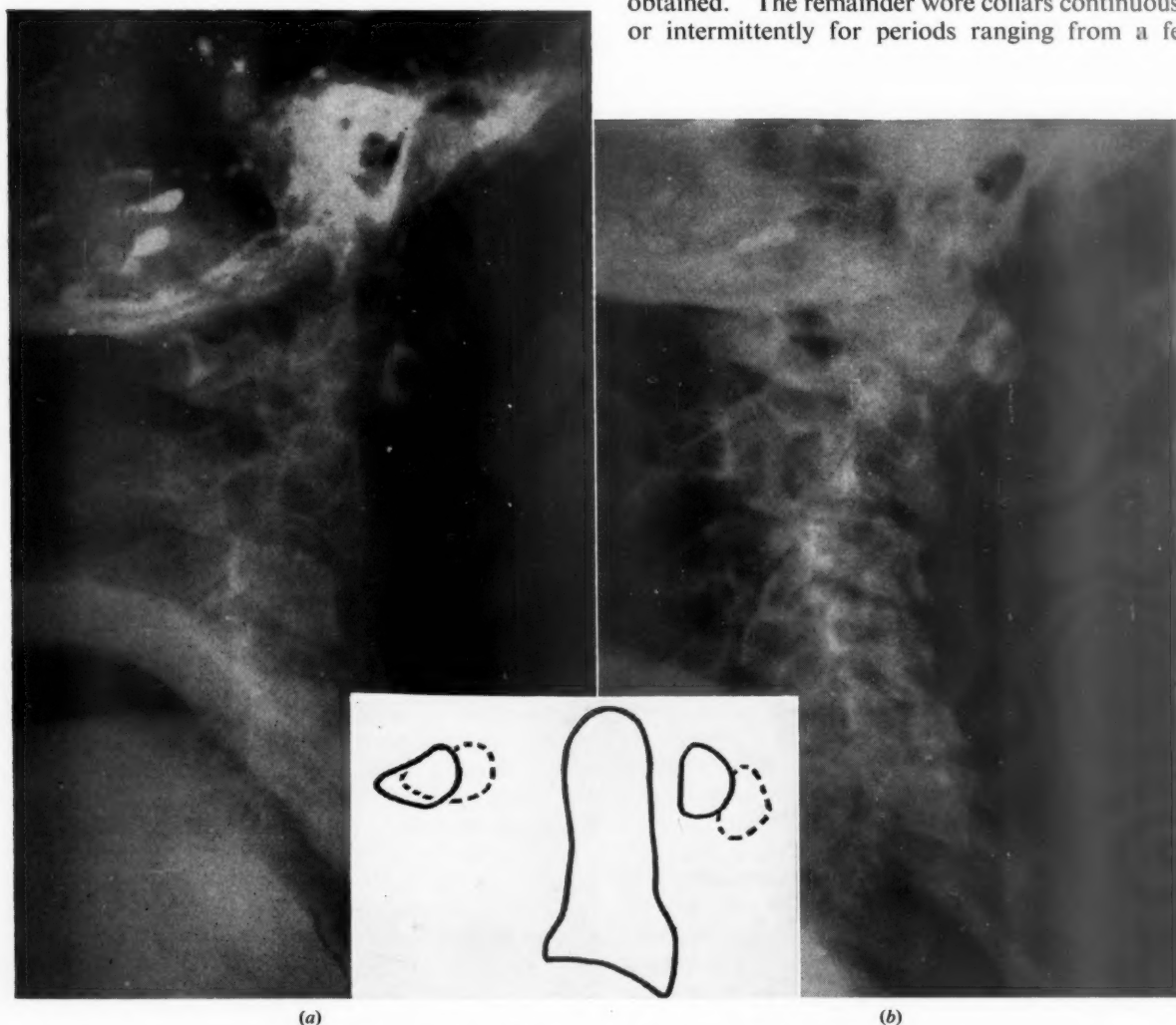


Fig. 11.—Case 27; radiographs in the second Minerva plaster.

(a) shortly after application; (b) one month later.

There has been a substantial increase in the forward displacement of the atlas in the interval.

weeks to 2½ years (Case 28). In four of them (Cases 24, 33, 43, and 44) the displacement was causing no symptoms though Case 24 had equivocal plantar responses. Each of the three patients followed up for from 4 to 25 months, continued symptom free and the displacements did not alter materially. The seven remaining rheumatoid patients treated by collars only all had pain from the displacement. In Cases 25, 28, and 29, pain was completely relieved. In Case 25 evidence of mild cord damage also disappeared during 23 months' observation, although radiologically there was little alteration in the displacement. In Case 28 the displacement became reduced and the abnormal mobility subsided over 2½ years, and in Case 29 also the abnormal mobility decreased over a period of 4 months. Cases 26, 37, and 46 derived good but not complete relief of pain. In Case 26 the displacement increased slightly over 20 months. In Case 37 the forward displacement remained constant but the antero-posterior traverse of the atlas on the axis decreased over 2 years and as a result reduction of the displacement became less complete in extension. Both Case 26 and Case 37 had equivocal evidence of cord damage and there was no evidence of deterioration in this respect. Case 46 was only observed for 2 months and had no further radiographs. Case 40 was averse to wearing a collar from the start and relief of pain in her case was less satisfactory than in the other patients; when steroid therapy was begun one month later there was considerable psychological and functional improvement, and she complained much less of pain from both the displacement and the arthritis. Her plantar responses remained equivocal.

(c) *Treatment by Occipito-Cervical Fusion.*—Two of the spondylitic patients (Cases 19 and 22), whose case histories are outlined in the Appendix had undergone occipito-cervical fusion elsewhere some years before being seen by us. Pain had been a prominent symptom in both cases and in Case 22 there was, in addition, evidence of severe cord damage which largely regressed after operation.

Nine other spondylitic and four rheumatoid patients underwent occipito-cervical fusion. Skull traction was maintained pre-operatively until radiographs revealed that no further reduction was occurring, and it was continued during the operation, which consisted of the insertion of an iliac crest autogenous bone graft extending from the occiput to the upper cervical laminae and spinous processes. Post-operatively, the traction was continued in some cases until the graft was united.

In others it was replaced by a Minerva plaster incorporating the skull callipers, and in one man, Case 15, by a "halo brace", until union had occurred. The patients carried out supervised limb and breathing exercises throughout the programme.

Pain from the displacement was present in each of the nine remaining spondylitic patients undergoing fusion and was the major indication for operation in four of them (Cases 10, 11, 17, and 21: Table VII). The operation completely relieved the pain in all cases. Cord damage was the main indication for operation in three patients (Cases 5, 9, and 12); in Cases 5 and 12 there was almost complete regression of the neurological changes after operation, and in Case 9 there was moderate improvement. Case 10 had evidence of mild cord damage and Case 21 equivocal evidence of cord damage which disappeared after operation.

As stated previously, the operation in Case 3 was mainly done because of severe deformity and in Case 15 because of the failure of supporting collars to control pain and prevent progression of the displacement.

In the four rheumatoid patients (Cases 30, 45, 47, and 48), the indication for operation was damage to the spinal cord. The post-operative course in Case 30 was complicated by infection of the donor site at the iliac crest and breakdown of the occipital incision, the bone graft failing to unite. During the first few post-operative weeks there was a temporary deterioration in his neurological status and as this was regressing the picture became complicated by the development of a peripheral neuropathy and of other features strongly suggesting disseminated vasculitis. He developed septicaemia and died 10 months after operation. In the others the results were very satisfactory and there was virtually complete neurological recovery in Case 45 and substantial improvement in Cases 47 and 48.

(d) *Treatment by Other Methods.*—Two spondylitic patients, Cases 6 and 13, had rotary subluxation of the atlas on the axis.

In Case 6, the more severe, a fixed deformity with the chin fully rotated to the right, was treated by traction in extension with an additional force applied to the right limb of the skull calliper to correct the rotation. During the 16 days of traction necessary to reduce the displacement there was a transient increase in the previously mild pyramidal signs. After reduction he was treated in two Minerva plasters, the first incorporating the skull callipers, and finally in plastic collar. On a film taken one year after discharge from hospital (Table VII), there was minimal forward displacement of the atlas with

lateral tilting. When examined 2 years after discharge, he had no cervical symptoms and there were only minimal residual pyramidal signs. Clinically and radiographically there was no movement in the upper cervical region and the atlanto-axial relationships were unchanged from those indicated in Table VII.

In Case 13 there was only a minimal rotary displacement, but this was causing intolerable, predominantly unilateral pain. This was immediately relieved by skull traction which was followed by plaster and then a cardboard collar for a few weeks. 34 months after treatment there had been no recurrence and the atlanto-axial relationships were radiographically normal (Table VII).

Discussion

Atlanto-axial displacement is a relatively common event in rheumatoid arthritis, the minimal prevalence in those members of the general population with any evidence of the disease being approximately one in thirty, in those with clinical evidence one in fifteen, and in those with disease sufficiently severe for them to be admitted to hospital almost one in five. In most cases the displacement is mild and, though few patients suffer serious harm from the lesion, it is important that it should be diagnosed, since an unstable displacement may progress and produce grave and occasionally fatal neurological complications. The frequency with which this lesion occurs in ankylosing spondylitis could not be determined from this study, but it is certainly less than in rheumatoid arthritis. It is, however, possible that it now occurs more frequently than formerly in ankylosing spondylitis as a result of the effective pain relief afforded to many spondylitic patients by x-ray therapy and other more recently developed agents, and because of the emphasis now laid on the importance of active movement in retaining mobility of the spine and limbs in this condition.

Clinical diagnosis of this complication is usually easier in ankylosing spondylitis than in rheumatoid arthritis where it may develop without any characteristic symptoms or striking physical signs. Active arthritis of the atlanto-axial joints usually results in upper cervical pain increased by sudden head movements and, when severe, the pain may radiate to the occipital, temporal, and frontal regions, but severe pain in these situations, particularly lancinating pains when the spine is jarred, as in riding in vehicles, should immediately arouse suspicion of abnormal atlanto-axial mobility. A complaint of the head "falling forwards" and of difficulty in

restoring it to the normal position voluntarily may be present with mild displacements which have produced no appreciable flattening of the occipito-cervical curve; difficulty in shaving under the chin may be an early symptom. Failure to appreciate the significance of such symptoms in some of the spondylitic patients studied had resulted in their having been given unwarranted and unsuccessful x-ray therapy.

The diagnosis ultimately rests on the radiographic demonstration of the abnormal relationship of the atlas to the axis. While in many instances there is a rotary component in the displacement, one facet of the atlas slipping further forwards than the other, in the great majority the main displacement is of the atlas forwards on the axis and the diagnostic radiological feature is an increase in the distance between the anterior arch of the atlas and the odontoid process. From the studies of the general population it would appear that after age 45, a gap of more than 3 mm. on a conventional single lateral radiograph is probably abnormal and highly likely to be associated with other evidence of an inflammatory polyarthritis, but that a distance of 4 mm. may be normal in younger subjects. Studies of hospital patients, however, suggest that in certain individuals a distance of 3 mm. may be abnormal and that even so small a displacement may be responsible for very severe pain. For certainty of diagnosis it is essential that a radiograph should be taken with the neck fully flexed, since one taken in the neutral position may fail to reveal a mobile displacement. A film with the neck extended is also desirable in order that the degree of abnormal mobility at the atlanto-axial level and also the possible presence of abnormal mobility at other levels in the cervical spine may be ascertained.

The major hazard of the lesion is damage to the medulla and spinal cord. The early indications of this can easily be missed or attributed to "functional overlay", particularly in patients with severe anatomical changes in the limbs and spine in whom neurological examination is difficult. Several patients in this series had had early symptoms of cord damage, in some cases for many months, the significance of which was only appreciated when more obvious neurological changes developed. The occurrence of cord damage is probably related not only to the extent of the displacement but also to the degree of abnormal mobility present. In view of the relatively much greater prevalence of atlanto-axial displacement in rheumatoid arthritis than in ankylosing spondylitis, it would appear that neurological complications of the lesion are more likely to occur in the latter condition. It is possible that

the erosion of the odontoid process observed more frequently in rheumatoid patients, by increasing the space available for the cord, may be one factor in this, but other important factors may be the greater ability of the cord to adapt itself to deformity of the spinal canal through the relaxing effect on the cord of the narrowing of multiple disks, a change commonly present in rheumatoid arthritis, and the tethering effect of the rigidity of the lower cervical region usually present in spondylitic patients.

Observation of the progress of some spondylitic patients would indicate that it is possible for the atlas to become stable in the displaced position, that a minor mobile displacement may become reduced, and that the abnormal mobility may subside without treatment. Spontaneous stabilization of a displacement was not observed in the rheumatoid patients in this series, but may occur in the deformed position if the inferior atlanto-axial joints become ankylosed (Ball, 1960). How often this occurs will be determined only by the long-term observation of larger numbers of patients. Meanwhile, early diagnosis of the displacement appears highly desirable not only that the patient may receive appropriate treatment to relieve any associated symptoms, but also that he may be protected from the risk of damage to the cord from minor trauma, particularly during physical treatment or anaesthesia. In any patient suspected of having such a displacement, or in any patient with severe rheumatoid arthritis undergoing general anaesthesia, radiographs taken with the neck gently flexed and extended are advisable. Those with minor degrees of displacement appear to be adequately protected by a supporting collar and this usually relieves any associated pain, but if there is intolerable pain unrelieved by this means, if the displacement progresses in spite of such support, or if neurological complications are present, reduction of the displacement and occipito-cervical fusion are indicated. This will relieve the associated pain and may be followed by remarkable regression of severe neurological changes.

Summary

From a study of radiographs of the cervical spine of samples of the general population it was concluded that after age 45 a separation of more than 3 mm. of the odontoid process from the anterior arch of the atlas on a conventional lateral film is usually abnormal and highly likely to be associated with rheumatoid arthritis, though in younger subjects a gap of 4 mm. may be normal. The

clinical studies suggest that occasionally a gap of even 3 mm. may be abnormal.

The prevalence of atlanto-axial displacement, so defined, in those members of the general population with any evidence of rheumatoid arthritis was 32 per thousand, in those with clinical evidence of the disease 64 per thousand, and in those with rheumatoid arthritis admitted to hospital 189 per thousand. The lesion was observed much less frequently in ankylosing spondylitis, but a definite prevalence rate could not be established from this study.

The clinical and radiographic features were studied of 22 patients with ankylosing spondylitis and 26 with rheumatoid arthritis who had developed spontaneous displacements of the atlas on the axis; it was found that in the spondylitic patients there was invariably some clinical evidence of the displacement but that this was absent in a substantial proportion of those with rheumatoid arthritis, the diagnosis in such cases being made only from routine radiographs taken with the neck extended and flexed; a mobile displacement was sometimes not apparent on a single lateral radiograph taken in the neutral position.

The characteristic clinical features of the displacement were:

- (1) Pain in the upper part of the neck radiating to the occipital and sometimes to the temporal and frontal regions, greatly aggravated by jarring movements.
- (2) Difficulty in getting the head back after looking downwards, often accompanied by difficulty in shaving under the chin and a sensation of "falling forwards" of the head.
- (3) Flattening of the occipito-cervical curve, often accompanied by some degree of torticollis.

In a few instances the presenting manifestations of the displacement were signs of damage to the spinal cord; in some of these the diagnosis presented great difficulty and in the first patient presenting in this way it was made only at autopsy. In all, six of the rheumatoid and seven of the spondylitic patients had evidence of cord damage. The severity of the neurological changes was roughly correlated with the degree of narrowing of the spinal canal, but some patients escaped damage to the cord in spite of a gross degree of displacement.

Spontaneous stabilization of the displacement may occur without treatment, but it is not known how often this occurs and in both conditions displacements were observed to progress in some untreated patients. The majority were therefore treated by supporting collars, usually with satisfactory relief

of pain and sometimes with reduction both of the degree of displacement and of the abnormal mobility. In one patient with rheumatoid arthritis, severe neurological changes had regressed following skull traction but there was progressive neurological deterioration after the application of a Minerva plaster followed by a block leather collar. Increase in the displacement during the period in plaster was observed.

Four of the rheumatoid patients were treated by occipito-cervical fusion, the indication for operation in each case being the presence of neurological signs. This was also the main indication in four of the eleven spondylitics who were treated by operation, the main indications in the others being pain in five, severe deformity in one, and progression of the displacement despite a collar in one. With the exception of one of the rheumatoid patients in whom fusion was unsuccessful and who later died from septicaemia, the results of operation were excellent; the local symptoms were relieved and there was major improvement in the neurological picture in those with cord damage.

With three exceptions, Cases 27, 47, and 48, the patients were under the care of Prof. J. H. Kellgren in the University Department of Rheumatism Research or of Mr. D. Lloyd Griffiths or Mr. John Charnley in the University Department of Orthopaedic Surgery in the Manchester Royal Infirmary. We are grateful to Dr. E. R. Bickerstaff of the Midland Centre for Neurosurgery, Smethwick, and to Mr. Robert Roaf of the Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, for permission to include Case 27, and to the late Dr. H. Stuart Barber of the Devonshire Royal Hospital, Buxton, and Dr. F. R. Ferguson and Mr. R. T. Johnson of the University Departments of Neurology and Neurosurgery, Manchester Royal Infirmary, for permission to include Cases 47 and 48. Two patients had been treated by cervical fusion for the dislocation before being seen by us, Case 19 by Mr. A. S. Kerr, and Case 22 by Mr. Sayle Creer, to whom we are indebted for information and for the loan of case records. Dr. R. Sykes supplied information about Case 12 who was initially under his care.

Dr. J. S. Lawrence, Director of the Empire Rheumatism Council Field Unit, gave us access to radiographs taken in connexion with surveys of the general population and also provided information regarding the prevalence of rheumatoid arthritis and ankylosing spondylitis in the samples studied. We are also indebted to Dr. J. Ball, who carried out the sheep cell agglutination tests both in the hospital patients and in the population studies.

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APPENDIX

Atypical Spondylitis

Case 19.—In 1945, at the age of 18, this man who had previously enjoyed excellent health developed painful stiffness of the neck mainly at night. After a month

his head "fell forward" and he developed intense pain radiating from the occipital to the temporal regions and back of the eyes, particularly on jarring movements such as those experienced when riding in buses. Atlanto-axial dislocation was diagnosed and he was treated by 10 weeks' halter traction followed by immobilization in plaster and leather collars for 7 months. At the end of this period he was symptom-free and had a full range of neck movement and he resumed his normal activities including sport. After 18 months, however, his symptoms recurred and in 1949 Mr. A. S. Kerr performed occipito-cervical fusion with complete relief. He was again symptom-free for 2 years but then developed mild stiffness and swelling of the left knee and some months later aching of the lumbar region; the latter was completely relieved by a spinal support. During the 6 months before he first attended the Rheumatism Centre in 1954 he had developed mild psoriasis and pain arising from the hip joints.

His spine was then painless but rigid apart from a trace of lower cervical movement. He had moderate flexion deformity and slight tilting of the head. His chest expansion was 6 cm. There was synovial thickening and effusion in both knees and mild painful restriction of hip movement. The sedimentation rate was 70 mm. in one hour (Westergren) and the sheep cell agglutination test was negative. Radiographs revealed changes in the sacro-iliac joints, pubic symphysis, and spine compatible with but not entirely typical of ankylosing spondylitis.

This condition was considered to be "atypical spondylitis" (Sharp, 1957), mainly on account of the mode of onset of the illness and the retention of normal cervical mobility after lengthy immobilization in the early stages; the complete relief of lumbar pain from use of a spinal brace, and the presence of psoriasis were also regarded as features unusual in ankylosing spondylitis.

He was given x-ray therapy to the hips with complete relief of pain and subsequently to the knees with some benefit. In 1957 a severe iron deficiency anaemia responded rapidly to parenteral iron. When he was last seen in 1958 there was still active but virtually painless arthritis in the knees; there had been slight loss of hip motion since 1954, but the spine was unchanged. There has been no recurrence of cervical symptoms and there were no neurological abnormalities.

Case 21.—When he was 18 years old and serving as a regular soldier in Palestine in 1938, this man developed generalized pain and stiffness in the trunk and limbs with swelling of the fingers. The onset was acute and he was febrile for the first few days. He was confined to bed for 2 months and remained in hospital for 3 months, making a full recovery. Some months later, in 1939, he had an attack of urethritis which cleared in 8 days with sulphonamides. In 1941 he developed painful swelling of the left foot and pain in the right shoulder region. He was admitted to hospital many times and was eventually discharged from the Army on medical grounds in 1945. The symptoms gradually abated and from 1948 to 1953 he was symptom-free and

leading a normal life. One year before his first attendance in September, 1954, he began to have attacks of pain in the low back and one or other buttock and groin; after 9 months these pains became continuous and he also had discomfort in both feet and in the shoulder regions. He had been breathless on effort and had had an intermittent productive cough for 2 years. He had not suffered from dysentery, eye trouble, or skin rashes.

On examination he was plethoric and obese, and had signs of bronchitis. The blood pressure was 175/115 mm. Hg. The left ankle jerk was sluggish. The lumbar spine was somewhat flattened, the dorsal and lumbar regions were rigid, and the cervical region was greatly restricted in motion. The chest expansion was 1 cm. The ankle, tarsal, and metatarso-phalangeal joints were diffusely thickened; the latter were dorsally subluxated and the right tarsus was painful and limited in motion. Both acromio-clavicular joints were tender with slight restriction of shoulder girdle movement, and there were focal tender areas on the iliac crests, left ischial tuberosity, and left acromion process.

The sedimentation rate was 73 mm. in the first hour (Westergren) and the sheep cell agglutination test was negative. Radiographically the sacro-iliac joints were fused and there was extensive ossification of spinal ligaments and disk margins, and periosteal new bone formation on the margins of the pelvis and plantar surface of the left os calcis. Squaring of the vertebral bodies (Rolleston, 1947) was absent.

This was classed as a case of "atypical" spondylitis, since it was felt that the patient was possibly suffering from Reiter's disease in an incomplete form.

After x-ray therapy to the spine and later to the left shoulder and right sterno-clavicular joints he was much improved. At a routine follow-up visit 2 years later, in 1957, the improvement had been maintained, though he was complaining of some pain in the upper cervical and sub-occipital regions principally in the mornings, but there was no radiographical evidence of atlanto-axial subluxation.

He requested an appointment in September, 1958, some months before his routine visit was due, as in the previous 6 weeks he had developed severe pain, typical of that of a mobile atlanto-axial displacement, and his head had become fixed in a flexed position and tilted downwards to the left. For the same period he had had intermittent paraesthesiae over the dorsum of the right foot although no definite sensory or other neurological abnormalities could be demonstrated apart from sluggish ankle jerks. Radiographs revealed forward subluxation of the atlas of moderate degree (Table VII).

The displacement was reduced by skull traction and from the time this was instituted he had no recurrence of paraesthesiae in the foot. When he was last seen, 9 months after occipito-cervical fusion, his spine was rigid and painless apart from very mild lower cervical pain and there were no neurological abnormalities.

Case 22.—A housewife who was aged 41 when she attended in 1954 had suffered repeated attacks of arthritis of the limbs and spine following intermittent throat

infections since the age of 11. She had severe mitral and aortic valvular lesions, complete rigidity of the spine, and hypermobility of most of her limb joints, but there was limitation of movement in the joints of the shoulder girdles and of the left index and medius. Cutaneous sensation was impaired in these fingers, which were wasted. It was suspected that spinal and cardiac changes might have resulted from recurrent rheumatic fever (Thomas, 1955; Sharp, 1957).

During an attack at age 29 her neck had become very restricted in movement and 4 years later she had gradually developed a severe atlanto-axial dislocation associated with pyramidal signs. This had failed to respond to prolonged immobilization and when she was aged 36 Mr. Sayle Creer and Mr. A. N. Guthkelch removed the posterior arch of the atlas and performed occipito-cervical fusion.

When she attended the Rheumatism Centre 5 years later after a further attack of polyarthritis, she had mild residual pyramidal signs and sensory changes in the left upper and lower limbs. She died from congestive heart failure at age 43.

Luxation spontanée atlanto-axiale dans la spondylarthrite ankylosante et l'arthrite rhumatismale

RÉSUMÉ

De l'étude des radiographies de la colonne cervicale des membres de la population générale on conclut que, à partir de 45 ans, un écart de plus de 3 mm. entre l'apophyse odontoïde de l'axis et l'arc antérieur de l'atlas, noté sur des projections latérales habituelles, est généralement anormal et très probablement associé à l'arthrite rhumatismale, bien que chez les individus jeunes un écart de 4 mm. puisse être normal. Des études cliniques font croire que, quelquefois, même un écart de 3 mm. peut être pathologique.

La fréquence d'un déplacement atlanto-axial, défini ci-dessus, chez des membres de la population générale présentant un signe quelconque d'arthrite rhumatismale était de 32 pour mille; chez ceux avec un tableau clinique d'arthrite rhumatismale cette fréquence était de 64 pour mille et chez des arthritiques rhumatisants hospitalisés elle s'élevait à 189 pour mille. Cette lésion se voyait moins souvent dans la spondylarthrite ankylosante, mais ce travail ne suffit pas pour en définir la fréquence exacte.

On a étudié les traits cliniques et radiologiques chez 22 malades atteints de spondylarthrite ankylosante et chez 26 malades atteints d'arthrite rhumatismale, ayant développé un déplacement spontané de l'atlas sur l'axis. On a trouvé que chez ceux atteints de spondylarthrite il y avait toujours des symptômes de déplacement, tandis que dans une proportion importante des cas d'arthrite rhumatismale de tels symptômes étaient absents et l'on arrivait alors au diagnostic à l'aide des radiographies prises avec la tête en flexion et en extension; quelquefois un déplacement mobile n'était pas apparent sur une seule radiographie latérale prise en position neutre.

Les traits cliniques caractéristiques du déplacement étaient:

- (1) Douleur dans la partie supérieure du cou, s'irradiant vers la région occipitale et quelquefois vers la région temporale et frontale, très aggravée par des secousses.
- (2) Difficulté à relever la tête après avoir regardé en bas, souvent accompagnée d'une difficulté à

se raser sous le menton et de la sensation que la tête "tendait à tomber en avant".

- (3) Aplatissement de la courbe occipito-cervicale, accompagné souvent d'un torticolis plus ou moins intense.

Dans quelques cas le déplacement se manifestait par des signes médullaires; dans certains de ces cas le diagnostic avait été très difficile et chez le premier malade on ne l'a fait qu'à l'autopsie. En tout, 6 malades rhumatisants et 7 malades spondylarthritiques ont présenté des lésions médullaires. La gravité des altérations neurologiques se rapportait au degré du rétrécissement de la moelle, malgré la magnitude du déplacement.

Un déplacement peut se stabiliser tout seul, sans traitement, mais on ne sait pas si c'est souvent le cas, et dans les deux maladies on a observé une aggravation constante du déplacement non traité. Pour cette raison on a traité la plupart des cas par des colliers, qui permettaient en général une diminution de la douleur et quelquefois du degré du déplacement et de la mobilité anormale. Chez un malade atteint d'arthrite rhumatismale, des altérations neurologiques graves ont rétrogressé après l'application de la traction sur la crâne; il y a eu une détérioration lorsqu'on a appliqué un plâtre Minerva suivi d'un collier massif de cuir. On a observé une augmentation du déplacement quand le malade était dans le plâtre.

Quatre malades rhumatisants furent traités par la fusion occipito-cervicale, l'indication de l'opération ayant été dans tous les cas la présence de signes neurologiques. L'indication principale fut la même dans quatre cas sur onze opérés de spondylarthrite; chez cinq autres on procéda à l'opération à cause de la douleur, chez un autre à cause d'une grave déformation et chez le onzième parce que le déplacement augmentait malgré le collier. A l'exception d'un malade atteint d'arthrite rhumatismale, chez qui la fusion avait échoué et qui mourut plus tard de septicémie, les résultats de l'opération furent excellents; les symptômes locaux furent soulagés et le tableau neurologique fut nettement amélioré chez ceux qui avaient une lésion de la moelle.

Luxación espontánea atlanto-axoidea en la espondilitis anquilosante y artritis reumatoide

SUMARIO

Del estudio de radiografías de la columna cervical entre miembros de la población general se concluye que, en edades superiores a 45 años, una separación de más de 3 mm. entre la apófisis odontoide del axis y el arco anterior del atlas, observada en proyecciones laterales corrientemente empleados, es usualmente anormal y muy probablemente asociada con artritis reumatoide, aunque en individuos más jóvenes una separación de 4 mm. puede ser normal. Los estudios clínicos sugieren que a veces una separación de solamente 3 mm. puede ser patológica.

La presencia de desplazamiento atlanto-axoideo, como expresado anteriormente, entre los miembros de la población general con algún síntoma indicativo de artritis reumatoide era 32 por mil, en aquellos con signos clínicos de la enfermedad 64 por mil, y entre los enfermos hospitalizados con artritis reumatoide la proporción fue 189 por mil. La lesión apareció con menos frecuencia en la espondilitis anquilosante, pero no es posible establecer en este estudio la proporción exacta.

Se estudiaron los rasgos clínicos y radiográficos en 22 enfermos con espondilitis anquilosante y 26 con

artritis reumatoide que habían desarrollado un desplazamiento espontáneo del atlas sobre el axis; en los enfermos espondílicos se vieron invariablemente signos clínicos de desplazamiento, ausentes, sin embargo, en un número considerable de enfermos con artritis reumatoide; en tales casos se llegó al diagnóstico solamente por radiografías regulares tomadas en flexión y extensión de la columna cervical; un desplazamiento móvil no se pudo ver a veces en una radiografía lateral tomada con el cuello en posición neutra.

Los rasgos clínicos característicos del desplazamiento fueron:

- (1) Dolor en la parte superior del cuello radiando a la región occipital y a veces a las regiones temporal y frontal, grandemente agravado por movimientos bruscos.
- (2) Dificultad para dirigir la cabeza hacia atrás después de haber estado mirando al suelo, frecuentemente acompañada de dificultad para afeitarse debajo de la barbilla y sensación de que la cabeza tiende a "caerse hacia adelante".
- (3) Aplanamiento de la curva occipito-cervical, acompañado frecuentemente por tortícolis en cierto grado.

En unos cuantos casos las primeras manifestaciones del desplazamiento fueron signos de lesión medular; en algunos de estos casos el diagnóstico fué muy difícil y en el primer enfermo que presentó este tipo de comienzo solamente se llegó al diagnóstico en la autopsia. En total, 6 de los enfermos reumáticos y 7 de los espondílicos presentaron evidencia de lesión medular. La gravedad

de las alteraciones neurológicas estuvo más bien en relación con el grado de aplastamiento de la médula que con el grado de desplazamiento.

Estabilización espontánea del desplazamiento puede ocurrir sin ser tratado, pero se desconoce la frecuencia con que esto ocurre y, por otra parte, en ambas enfermedades en algunos enfermos el desplazamiento no tratado tendía a empeorar. La mayoría de los casos fué por lo tanto tratada con soportes del cuello, usualmente con satisfactoria disminución del dolor y algunas veces con reducción del grado de desplazamiento y de la anormal movilidad. En un enfermo con artritis reumatoide, alteraciones neurológicas graves regresaron tras tracción continua del cuello, apareciendo un empeoramiento neurológico progresivo tras la aplicación de un Minerva de yeso seguido de un soporte de cuero continuo para el cuello. Aumento del grado de desplazamiento durante el período de tratamiento con yeso ha sido observado.

Cuatro de los enfermos con artritis reumatoide fueron tratados por fusión occipito-cervical, considerándose como indicación para el tratamiento operativo la presencia de signos neurológicos. Esta misma fué la principal indicación en cuatro de los once enfermos espondílicos tratados operatoriamente, siendo la principal indicación en los otros: dolor en cinco, grave deformidad en uno y aumento del desplazamiento a pesar del soporte del cuello en uno. Con la excepción de uno de los enfermos con artritis reumatoide, en quien la fusión fracasó quien falleció más tarde de septicemia, los resultados de la operación fueron excelentes; los síntomas locales mejoraron y en los enfermos con lesión medular el cuadro neurológico mejoró más notoriamente.

EXPERIMENTS WITH CONTROL SUBSTANCES

BY

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Even the least sceptical agree that a large proportion of research upon therapeutic substances turns out to be research about placebos. Recent estimates based on American observations suggest that 30 per cent. of currently advertised remedies are dropped by their makers each year. Not all these are dropped because experience shows that they have no direct pharmacological action; some are no doubt withdrawn because they are toxic. Further, not all remedies that are well-known to be useful are extensively advertised, and so the estimate is therefore too high as a measure of the proportion of substances in present use that are in fact placebos. But perhaps 15 per cent. would be a conservative estimate of the number of inactive substances discovered to be so and dropped each year: even so, about 39 per cent. of substances in current use would be found to be inactive within 3 years, and half the entire manufacturers' lists would be turned over for this reason alone within 5 years. On the other hand, new brands of drugs with certain kinds of central action (the so-called "tranquillizers") are being introduced in such volume that they double in number about every 2 years. It is therefore necessary to investigate the placebo effect deliberately, efficiently, and experimentally, since it is clearly to this factor that so many new substances owe their initially impressive but transient effect.

Pepper (1945) pointed out that, though the placebo had been known for hundreds of years as a powerful therapeutic agent, the textbooks were silent about its mode of action and the journals contained no papers in which it was treated as an object of research in its own right. Whether his note stimulated the development of such an interest or itself reflected it, it appears superficially that the situation has changed since that time. Starting about 8 years ago, the abstracting services have

listed between ten and twenty papers a year that contained the word "placebo" in the title; it is the purpose of the present paper to point out that, although Pepper's note was followed by an apparent spate of work upon the subject, we still know almost nothing about the pharmacology of the placebo: not even about the indications and contra-indications for its use.

For this there are three main reasons: The first is that perhaps two-thirds of the papers since 1945 have described specific treatments that were compared with a placebo as control, and in such cases information about the behaviour of the placebo itself is only incidentally available. Secondly, most of the remaining papers have been reviews of a field which is not yet ripe for review because too few facts are known. Thirdly, so little *is* known, not merely because there have been few attempts to obtain experimental evidence, but because the idea of placebo is a pseudo-unitary concept, and to make useful statements upon the pharmacology of the placebo is probably even more difficult than to make such statements about *the* pharmacology of substances that affect water balance.

It is not that saline, lactose, chalk, or substances given in homoeopathic doses necessarily show many interesting points of dissimilarity in their actions upon the psyche, although there are indeed some: size, colour, vehicle, taste, and route are certainly important determinants of placebo effect. These points are so reliably established and so frequently seen by everyone interested in the phenomenon that many have thought that there was nothing more to be known about placebos. The point of the analogy with substances that affect water balance is not that there are many such substances, but that they have many modes of action and many target organs. In the context of placebos, this is to say that there are many kinds of placebo reaction and many kinds of individual to display them.

We may distinguish, broadly, positive and nega-

* Read by Dr. B. G. Adams in the absence of the author at a meeting of the Heberden Society at the London Hospital on September 16 1960.

tive reactors (and reactions) and also non-reactors. Positive reactors are those who produce reactions that are in the desired or "therapeutic" direction, in the clinical situation; negative (sometimes called "paradoxical") reactors those who react in a way opposed to that desired. Non-reactors give no reaction at all to the ingestion of pharmacologically inert substances. Experiments can also be carried out in the laboratory, and reactors and non-reactors are found here as well. But the terminology poses some problems: positive reactions might be defined as those that oppose the displacement from the normal state produced by the stress of an experimental procedure, and negative reactions might be defined as displacements from the normal produced by the so-called placebo (or, in the experimental situation, the "dummy") itself. An example of the first case is the analgesia that often follows the administration of a dummy to a subject suffering experimentally-produced pain; of the second, reports of symptoms not experienced until the dummy was given to a subject who was under no stress other than the administration of the dummy itself.

But to define negative and positive reactions in this way does not of course mean that they share the mechanisms of clinical negative and positive reactions; and, indeed, one of the first problems to clarify, since it is often helpful to take a new medical question into the laboratory at an early stage, is whether the basis of reactions produced in presumably healthy subjects can legitimately be compared with those seen in patients. There are some grounds for thinking so, although this has not yet been tested directly. Lasagna, Mosteller, von Felsinger, and Beecher (1954) were the first to point out that the "personalities" of clinical reactors and non-reactors to placebos given for pain following major surgery differed in ways that could be measured. Interviews by psychiatrists, ratings by hospital staff, and scores on Rorschach tests agreed in suggesting strongly that the reactors were "not whiners or nuisances, not typically male or female, young or old and (they) had the same average intelligence as the non-reactors . . . all considered the hospital care 'wonderful' whereas (few) non-reactors felt this way. The reactors tended to ask less frequently for medications and to be more cooperative . . . The reactors also tended to have more 'somatic' symptoms . . . during periods of stress . . . There was a definitely greater use of cathartics . . . they tended to be more emotionally expressive and . . . to speak freely, most frequently of themselves and their problems . . . they were more frequently active church-goers . . . and had

less formal education". They also "liked everyone". It is perhaps not surprising to us, after learning that reactors are not whiners, that hospital staff who attempted to guess which patients were reactors and which were not guessed wrong more frequently than they guessed right.

These were American surgical patients, aged between 20 and 79. In the laboratories of this medical school the reactions to dummies of healthy British medical students aged 18 to 30 have been experimentally investigated for some time.

Instead of Rorschach and psychiatric interviews, we used conventional pencil and paper personality tests, and background information collected during routine investigations. Briefly, it turned out that the experimental reactors (that is to say, those subjects who thought that they had taken an active drug when in fact they had received only a dummy) were more aware of social pressures, more extroverted, less "dominant", and more neurotic than the non-reactors. They rated their performance less highly in classwork and were in general less self-confident. They had not, it appeared, more previous experience with drugs than non-reactors, but they did show a greater expectancy that any drug would have more effect upon them than did the non-reactors. They also had higher resting pulse rates than the latter, and their pulse rates were more labile under stress.

However, the basic question is whether there is or is not such a person as a *consistent* placebo reactor and such a person as a consistent non-reactor. Wolf (1959) failed to show in his own experimental studies that the occurrence of reactions in a very small group of experimental subjects followed anything other than a chance distribution, and for his group this was no doubt true. However, to this field perhaps more than to any other applies Delisle Burns's dictum that people working on the central nervous system should declare their bias in advance (Burns, 1958): so, perhaps because we expected to find a greater degree of patterning in the responses than chance would lead one to predict, we indeed found this to be so (Joyce, 1959). It turned out that predictions about the category to which a given healthy subject would belong when he was tested with the crucial administration of a dummy could be made with an accuracy of between 60 and 80 per cent., depending upon the kind of antecedent test used to make the prediction. These figures are far from the desirable and certainly unattainable 100 per cent. success, but they are very much better than would have been expected to occur by chance. The experiment has been repeated in part with a group of rather older

American medical students in the Middle West . . . and their reactions can also be predicted using the tests developed in London, with just about the same degree of accuracy. For responses to be predictable they must clearly be consistent, and it seems that consistency can be attained under suitable conditions. Failures to demonstrate consistency suggest that the conditions, whatever they are, are not present. A better test, of course, is to see whether, using the experimentally derived tests again, predictions can be made about the outcome in a clinical situation. This is being done at the moment in a sample of out-patients with rheumatoid arthritis.

Just as there is more than one placebo substance and more than one kind of reaction, so there are many clinical situations and many kinds of patient. There are presumably some differences in the personalities of those who become hypertensive, develop gastric or duodenal ulcers, or show skin reactions to stress. In addition, it may be that some members of any group are more highly motivated to recover their healthy state, and their reactions to a placebo may be an index of this. Hankoff, Engelhardt, and Freedman (1960) find that this is certainly true for schizophrenic post-hospitalized out-patients; those who show positive placebo responses during prolonged administration are much more likely to remain well for significantly greater periods of time thereafter. Something of the same kind emerges from comparisons of the response of various kinds of chronic out-patient groups to vitamin B₁₂ given as a "tonic" (O'Brien, 1954). This author's findings about the kind of patient with the kind of history that was most promising, however, could not be separated from his findings about the kind of physician with the kind of personality that was most effective, because the same physician always treated the same group of patients.

Some attempts have been made by others to disentangle these factors, but it would be a fair summary at the present time to say that little more has been achieved than the experimental substantiation of some common-sense clinical impressions: that the doctor himself must be persuasive, have confidence in his remedies, and be acceptable to the patient. But it is becoming quite clear that drugs *known* to be "active" also require these and other supports if their actions are, in fact, to be shown. There is reasonably good evidence that a great many drugs, and not only those that probably act upon the more psychologically accessible parts of the brain stem, show their so-called "characteristic" actions only if the manner of their presen-

tation allows them to do so. Ipecac. can inhibit as well as cause vomiting; atropine can increase gastric motility; phenobarbitone can increase and dexamphetamine decrease the general level of activity; and so on. It also appears from a very interesting study by Uhlenhuth, Canter, Neustadt, and Payson (1959) that the true differences between meprobamate and phenobarbitone on the one hand and a placebo on the other, in a clinical trial with anxious out-patients, only emerge if the physician conveys his expectation that *some* remedy used in a double-blind trial will be useful to the patient. If he is too detached, and manifests no such optimistic expectation at all, no differences are found.

Knowles and Lucas (1960), in one of the very few laboratory investigations of the placebo response so far published, draw attention to another factor that profoundly modifies the situation: this is the presence or absence of other subjects when the treatment is given and the responses to it recorded. Their reactors to dummies had a higher "neuroticism" score on the Maudsley Personality Inventory than did their non-reactors if the dummy was given to groups of three subjects at a time; but those who were reactors showed no differences in "neuroticism" scores when the substance was given to them individually. On the other hand, individual treatment gave reactors with higher "extroversion" scores; whereas when treated in groups of three, reactors and non-reactors did not differ on this measure.

One might speculate at length about the reasons for these findings. Their practical importance, however, is unmistakable, because drugs and placebos are given in the hospital ward under something that approximates to group conditions, and in out-patient or private practice for consumption at home under something like individual conditions. Here the circumstances are, of course, "contaminated", because other patients or friends or members of the family are receiving different treatments or none at all; and Nowlis and Nowlis (1956), in some suggestive work that they have unfortunately discontinued and published little about, have shown us that the presence in a group treated with one active substance of a member treated with another produces some very unexpected results in all of them. Starkweather (1959) and Goldstein, Searle, and Schimke (1960) find similar effects, although different in direction.

In a long, so far unpublished paper, A. J. Young of Leeds has considered other relationships between personality factors and reaction tendencies in arthritic out-patients. His groups are small and his measures many, but his results suggest that

positive reactors ("improved patients" in his terminology) are introverted and neurotic and that negative reactors ("adversely affected patients") are dominant. He also finds that both kinds of reactor are likely "to be suffering from an arthritis precipitated by an emotional stress". He proposes that somatic changes, whether related to a disease process or to relatively acute or short-lasting chronic events such as drug administration, are more likely to occur in such people because of psychological rather than physiological events. This is an artificial dichotomy, and the factor, he believes, is not a simple one; but it agrees with our own view that reactors are more sensitive to what we may call "information" of all kinds—whether this arises from their environment, from others in their context (such as doctors and other patients or subjects), or their own viscera. We are at present trying out some ideas about the ways in which reactors and non-reactors handle sense-data of different kinds.

We scarcely know more as yet than that under some specified conditions the placebo will "work" reliably, but this is a valuable start. It seems that improvement in the definition of these conditions, for which both laboratory and clinical experiment will be necessary, is extremely likely to give valuable practical results.

Summary

Little is known of the pharmacology of the "placebo", partly because there are so many different kinds of placebo which vary in their actions, and partly because there are so many different kinds of individuals to react to them. Placebo reactors can be divided into "positive reactors", who produce reactions in the desired or therapeutic direction, "negative reactors", who react in a way opposed to that desired, and "non-reactors", who show no effect at all. Reactors are more aware of social pressures, more extroverted, less dominant, and more neurotic than non-reactors. They are also less self-confident and show a greater expectancy that the "drug" will be effective. Modes of presentation of active drugs and placebos in clinical trials are also important. The effect of the administration of a drug in hospital may differ from that of a drug administered in general practice because the former is given to a patient who is one of a group, and the latter to an individual acting alone.

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Discussion.—DR. J. H. GLYN (London): Would it be interesting to relate the response of positive reactors to "hypnotizability"? There must be some common factor of suggestibility and this would be a good start.

DR. ADAMS: There is no positive correlation between the number of people reacting positively and their suggestibility. Whether that is the same thing I do not know.

DR. V. WRIGHT (Leeds): This is a subject in which Prof. Hartfall has been interested for some time. A study was carried out with the intra-articular therapy, and it was observed that 36 per cent. of our patients claimed improvement; arising from that work, we began further studies. Dr. Young and Dr. Morrison interviewed all patients, taking a full psychological history, and then gave a course of placebo tablets. Some patients claimed improvement from injections rather than from placebo tablets—one would anticipate this. It was found also that those at the Maudsley who had improved were more neurotic and introverted. The most interesting point was that when we came to assess the correlation between side-effects and placebo response, patients who were consistent non-reactors failed to show side-effects at any time, and this was statistically significant at the 1 per cent. level of probability. It seems possible that, if one is anxious to know in a trial which patients will show side-effects, one may give a week's course of placebo tablets, and observe those who develop side-effects. This would show who were reactors in the group and would enable a highly selected group on which to work to be chosen.

Expériences avec des substances de contrôle

RÉSUMÉ

La pharmacologie du "placebo" (*substance inerte ou substance-temoin*) est peu connue. Les sujets recevant des "placebos" peuvent être divisés selon leur réaction en "positifs", "négatifs" et "non-réagissants". Les "positifs" réagissent dans le sens désiré ou thérapeutique, les "négatifs" réagissent dans le sens contraire et les "non-réagissants" n'accusent aucun effet. Les sujets qui réagissent aux "placebos" sont plus susceptibles aux pressions sociales, plus extrovertis, moins dominants et plus névrosés que les autres. Ils ont aussi moins de confiance en eux-mêmes et plus d'espoir

que le "médicament" sera efficace. La présentation du médicament actif et du "placebo" dans les essais cliniques est aussi importante. L'effet de l'administration du médicament à l'hôpital peut être différent de celui du médicament administré, par un praticien, parce qu'à l'hôpital le malade reçoit son traitement comme membre d'un groupe, tandis que, quand il est soigné par son médecin, il doit agir seul.

Experimentos con sustancias de control

SUMARIO

Poco se conoce acerca de la farmacología del "placebo" (*substancia inerte o testigo*), debido en parte a la gran cantidad de formas con acciones variables y en parte a la manera diferente en que cada individuo puede reaccionar tras su administración. Los sujetos pueden

dividirse en relación con su modo de reacción al placebo en "positivos", los que presentan reacciones en la dirección deseada o terapéutica; "negativos", los que reaccionan de un modo opuesto al deseado y "no reactivos", los que no desarrollan efecto alguno. Los individuos que reaccionan a placebos son más concientes de las presiones sociales, más extravertidos, menos dominantes y más neuróticos que los demás. También presentan menos confianza en sí mismos y demuestran una mayor esperanza en la efectividad del "fármaco". El modo de presentación tanto del fármaco activo como del "placebo" en las pruebas clínicas es igualmente importante. El efecto de la administración de una droga en el hospital puede diferir de aquel en práctica general, porque en el primer caso el fármaco se administra a un enfermo que es una unidad en un grupo, y en el segundo caso a un individuo actuando solo.

TISSUE MAST CELLS IN THE BONE MARROW IN RHEUMATOID ARTHRITIS

BY

P. C. MCCREA

Royal City of Dublin Hospital, and Department of Pathology, Trinity College, Dublin

Mast cells are connective tissue cells of the histiocytic family. They are characterized by the presence of large cytoplasmic granules which stain metachromatically with dyes such as toluidine blue, in which respect they resemble blood basophils. Tissue mast cells are present in the connective tissue of many species, especially in the walls of blood vessels and the immediate adjacent connective tissue (*Brit. med. J.*, 1956).

The significance of tissue mast cells in human bone marrow is uncertain. Rohr (1949) found tissue mast cells in the bone marrow in hypoplastic and aplastic conditions only. Fadern (1951), in a study of 2,800 cases, found mast cells in seven cases, three of which showed severe marrow depression. Williams (1952) and Johnstone (1954), who examined marrows from patients suffering from a wide variety of pathological conditions, found mast cells in 17 and 70 per cent. respectively. Two of the patients in Johnstone's series suffered from rheumatoid arthritis, although in one of them the disease was classified as atypical. Mast cells were demonstrated in both cases and were present in unusually large numbers in the atypical case.

The purpose of the present investigation was to study the mast cell content of the bone marrow in patients suffering from active rheumatoid disease and anaemia. These patients formed part of a group in which the relationship between marrow iron content and response to intravenous iron therapy had been investigated previously (McCrea, 1958). It was possible, therefore, as a supplementary study, to determine whether the presence or absence of mast cells from the bone marrow was of prognostic significance regarding the effect of intravenous iron therapy.

Materials and Methods

Twelve in-patients suffering from active rheumatoid arthritis and a moderate degree of anaemia were

examined. In each case the initial haemoglobin level was less than 11.2 g./100 ml. (70 per cent.). In an earlier investigation of bone marrow iron content (McCrea, 1958), sternal marrow was aspirated from these patients and histological sections were prepared, using a modification (Hutchison, 1953) of the technique described by Cappell, Hutchison, and Smith (1947). Further sections were prepared from the same blocks and were stained with 0.01 per cent. toluidine blue to demonstrate mast cells. Tissue mast cells and basophil leucocytes both contain granules with metachromatic staining properties, but Johnstone (1954) has pointed out that the granules of the latter cells are extremely soluble in water and alcohol and are, therefore, not seen in fixed tissue sections when an aqueous or alcoholic fixative has been used.

Mast cells are usually rounded or ovoid, although bizarre forms with elongated cytoplasmic processes are sometimes seen. The granules often overlay the nucleus tending to obscure it (Johnstone, 1954). In each case, several marrow fragments were examined microscopically for mast cell content and the marrows were roughly classified as follows:

- No mast cells present.
- + Scanty mast cells present but not more than one per high-power field.
- ++ Moderate number of mast cells present, more than one but less than five per high-power field.

Results

Marrow mast cells were reasonably plentiful in one patient (Case 6), scanty mast cells were present in five cases, and in the remaining six, no mast cells were demonstrated (Table, overleaf). Mast cells, when present, were irregularly distributed throughout the marrow fragments and sometimes a mast cell was present in one fragment, whereas another fragment of the same marrow contained no mast cells.

TABLE
FINDINGS IN STERNAL MARROW IN TWELVE CASES

Case No.	Tissue Mast Cells	Marrow Iron	Response to Intravenous Iron Therapy*
1	+	+	—
2	+	+	—
3	+	+	—
4	+	+	—
5	+	+	—
6	++	—	+
7	—	—	+
8	—	—	+
9	—	+	—
10	—	+	—
11	—	+	—
12	—	+	—

* Increase in haemoglobin of at least 2 g. per 100 ml. over a test period of one month.

There was no constant relationship between the presence or absence of marrow mast cells, marrow iron content, and response of the anaemia to intravenous iron therapy (Table). Mast cells were demonstrated both in marrows which contained iron and in those which did not. Conversely, in some marrows which contained iron and in some which were devoid of iron, no mast cells were seen. The anaemia in one patient (Case 6) in which marrow mast cells were most plentiful responded to iron therapy. Cases refractory to iron therapy included a number whose marrows contained mast cells and some whose marrows showed no mast cells. The anaemia in two cases, in which neither marrow mast cells nor marrow iron were demonstrated, improved after iron therapy (Table).

Discussion

Mast cell granules contain heparin (Jorpes, 1946) and there is strong evidence that the granules contain histamine as well (Riley and West, 1953). Rohr (1949) and Fadern (1951) suggested that the presence of mast cells in the bone marrow indicated marrow depression in some form. Fadern felt that the marrow inhibition was partly due to the inhibitory effect of heparin upon local cell growth, and concluded that tissue mast cells are abnormal constituents of bone marrow. Johnstone (1954), however, who examined a large number of patients suffering from a wide variety of pathological conditions, considered that mast cells were a normal constituent of human bone marrow and that their

absence in 30 per cent. of his cases was probably governed by the selection inevitable in a small sample of marrow. Riley (1959) felt that tissue mast cells in human bone marrows had the same significance as elsewhere, and that they were a normal constituent of the connective tissues.

Johnstone (1954) examined two cases of rheumatoid arthritis. Mast cells were present in the marrow in each case and in one, which was classified as atypical rheumatoid, mast cells were present in unusually large numbers. Mast cell proliferation to this degree was not seen in the present series and, indeed, mast cells were scanty or absent in all but one of the marrows examined.

Johnstone (1954) was unable to find any correlation between the iron content of the marrow and the presence or numbers of mast cells there. The results of the present study agree with Johnstone's observations in this respect. The presence or absence of mast cells from the bone marrow was of no value in forecasting the results of intravenous iron therapy. The anaemia in Case 6 responded to intravenous iron therapy though marrow mast cells were most plentiful, and cases refractory to iron therapy included some whose marrows contained mast cells and some whose marrows contained none.

Marrow mast cells were not demonstrated in half of the cases studied. Their absence may possibly have been due to a sampling error on account of the small pieces of tissue examined. The presence or absence of mast cells is not related to marrow iron content or to the success or failure of intravenous iron therapy. It would appear that the presence of these cells in small numbers or their absence from marrow samples in anaemic patients with rheumatoid arthritis is of little significance.

Summary

Sternal bone marrows from twelve patients suffering from active rheumatoid arthritis and anaemia were examined for mast cell content.

In five cases scanty mast cells were present, in one the marrow contained a moderate number of mast cells, and in six no mast cells were demonstrated.

There was no constant relationship between the presence or absence of marrow mast cells, marrow iron content, and response of the anaemia to intravenous iron therapy.

I am grateful to the medical staff of the Royal Bath Hospital, Harrogate, where this study was undertaken, for their co-operation. Dr. J. V. Wilson was most helpful, and Mr. H. Gibson, F.I.M.L.T., gave valuable technical assistance.

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Mastzellen tissulaires dans l'os des malades atteints d'arthrite rhumatismale

RÉSUMÉ

La moelle osseuse du sternum fut examinée chez douze malades atteints d'arthrite rhumatismale évolutive

accompagnée d'anémie pour y rechercher des mastzellen.

Dans cinq cas on trouva quelques mastzellen, dans un cas on en trouva quelques-unes et dans six cas on n'en trouva aucune.

On ne trouva aucun rapport constant entre la présence ou l'absence des mastzellen dans la moelle osseuse et la teneur en fer de la moelle et la réponse de l'anémie à la thérapie martiale intraveineuse.

Mastocitos tisulares en la médula ósea de enfermos con artritis reumatoide

SUMARIO

Médula ósea del esternón fué examinada en doce enfermos con artritis reumatoide evolutiva, acompañada de anemia, para estudiar su contenido en mastocitos.

En cinco casos se encontraron mastocitos escasos, en uno se vió un número moderado de ellos y en seis casos no se encontró mastocito alguno.

No hubo relación constante entre la presencia o ausencia de mastocitos en la médula ósea por un lado y el contenido de hierro en la médula y la respuesta de la anemia a la feroterapia intravenosa por el otro.

CORTICOSTEROID BRUISING

BY

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Unprovoked bruising and excessive bruising following only moderate trauma has become, in recent years, a familiar complication of prolonged corticosteroid therapy. Nashelsky and Smyth (1958), reviewing the subject, showed that the lesions were not due to altered capillary fragility or to a clotting defect. Scarborough and Shuster (1960) studied biopsy material from "corticosteroid purpura" and showed that at the site of the lesions there was a loss, and a disorganization, of dermal collagen.

At a recent corticotrophin conference the opinion was expressed that this pathological bruising did not occur in corticotrophin-treated patients (West, 1960). The purpose of this paper is to substantiate this opinion and to discuss the implications.

Patients.—During the last year 58 patients at one particular follow-up clinic who satisfied the following requirements were examined for evidence of pathological bruising:

- (1) They were suffering from rheumatoid arthritis or ankylosing spondylitis without any complicating disease of note.
- (2) They had been receiving *corticosteroid* therapy for at least 2 years at a mean dose level of 7.5 mg. prednisolone or more, or an equivalent dose of triamcinolone or dexamethasone.

or

- (3) They had been receiving daily injections of *corticotrophin* gel for at least 2 years at a clinically effective dose level confirmed by repeated urinary assays for total 17-hydroxy-corticosteroid (17(OH)CS).

Criteria of Pathological Bruising

- (1) Multiple bruises of the senile purpuric type, seen typically on the forearms;
and/or
- (2) Multiple unprovoked bruises taking 3 weeks or more to clear;

also in some cases

- (3) Excessive bruises to moderate trauma on the legs or feet, with blood blister formation leading to breaks in the skin and ulcers.

Results

The findings in the 58 patients are shown in Table I.

TABLE I
FINDINGS IN 58 PATIENTS

Treatment	No. of Cases	Pathological Bruising			
		Present		Absent	
		No.	Per cent.	No.	Per cent.
Corticosteroids ..	40	24	60	16	40
Corticotrophin ..	18	0	0	18	100
Total ..	58	24		34	

The influence of sex, age, duration of disease, duration of therapy, dosage, etc., have been analysed as follows:

- (1) **Sex and Age Distribution.**—The results are shown in Table II.

TABLE II
INCIDENCE OF BRUISING, BY AGE AND SEX

Treatment	Sex	Pathological Bruising		Age (yrs)	
		No.	Per cent.	Mean	Range
		Present	Absent		
Corticosteroids	Female	20	83	48*	30-65
		4	17	42	30-60
	Male	4	20	56½	52-61
		16	80	48½	33-70
Corticotrophin	Female	8	100	42	38-49
	Male	10	100	41½	19-57

* Six of the affected females were under 40 years of age.

- (2) **Duration of Disease.**—In affected females the mean duration was $15\frac{1}{2}$ years, and in the unaffected females 13 years. In affected males the mean duration was $12\frac{1}{2}$ years, and in the unaffected it was 12 years.
- (3) **Duration of Therapy.**—In affected patients (all on corticosteroids) the mean duration was $5\frac{1}{2}$ years; in unaffected patients on corticosteroids it was also $5\frac{1}{2}$ years, and in those on corticotrophin it was $4\frac{1}{2}$ years.
- (4) **Mean Dosage in Last 2 Years.**—In the corticosteroid group, the mean dose (as prednisolone) was 10 mg. for the affected and 9.3 mg. for the unaffected. In the corticotrophin group the mean dose (as 17(OH)CS excreted daily) was 22 mg.
- (5) **Disease Activity and Physical State.**—Between the affected and unaffected groups of females there was little difference if any in respect of mean erythrocyte sedimentation rate, haemoglobin, strength of grip, blood pressure, weight, or functional capacity. The mean total white blood count in the affected group was 10,600 and in the unaffected 7,750. It did appear that patients with the most severe and damaging leg bruising had higher total white counts (11,000-14,000) and had received more corticosteroid than the mean for the group.
- (6) **Adrenal Suppression and Corticosteroid Therapy.**—The adrenal output of cortisol (hydrocortisone) can be assessed by measuring the urinary excretion of total 17(OH)CS and deducting the contribution made, if any, by the dose of exogenous corticosteroid.
The mean adrenal contribution to 17(OH)CS in thirteen affected patients was 5.3 mg. (range 2.5-9); in twelve unaffected patients it was 7 mg. (range 4-11).
- (7) **Effect of Change of Therapy.**—Three affected women changed from oral corticosteroid to corticotrophin during the period of observation. One stayed on corticotrophin for 1 month and was sure that her "bruisability" decreased. The other two have now been on corticotrophin for more than 6 months and have had no pathological bruises during this time.

Discussion

There is no doubt about the reality of this striking difference between oral exogenous corticosteroid therapy and corticotrophin therapy, at least at the

dose levels used at this Centre. Savage has found the same difference at the West London Hospital (personal communication). The bruising is at times a serious complication when the skin of the leg breaks down, and it cannot be assumed that the skin and subcutaneous tissues are the only connective tissues involved. It is therefore of some importance that the cause and a remedy be found. The defect may be due either to a direct action of the exogenous corticosteroid on the connective tissue, or to the loss of an adrenal hormone or of the adrenocorticotrophic hormone, occasioned by the administration of the exogenous corticosteroid. If an elevated level of circulating cortisol can, in time, cause the pathological bruising, its absence during corticotrophin therapy may be due to the concurrent secretion of a compensating adrenal hormone or of corticotrophin.

If the lesions result from a relative lack of the adrenal androgen, substitution therapy may provide a remedy. This possibility needs investigation. Two of the affected females referred to above received methandrostenolone (Dianabol) 10 mg. daily for 6 months without improvement.

Summary

Over the period of a year, 58 patients receiving long-term corticosteroid therapy for rheumatoid arthritis and ankylosing spondylitis have been examined repeatedly for evidence of pathological bruising. Of forty receiving exogenous corticosteroids, 60 per cent. had pathological bruising and of eighteen receiving corticotrophin none was so affected.

The pathological bruising of long-term exogenous corticosteroid therapy can be a serious complication. (It is hoped that the above findings may provide a clue to its remedy.)

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Ecchymoses corticostéroïdes

RÉSUMÉ

Pendant un an, 58 malades atteints d'arthrite rhumatismale et de spondylarthrite ankylosante et soumis à un traitement prolongé par des corticostéroïdes, furent examinés à plusieurs reprises en recherchant des ecchymoses pathologiques. On en trouva chez 60% des 40 malades traités par des corticostéroïdes exogènes, mais on n'en trouva aucune chez les 18 malades restants traités par la corticotropine.

Les ecchymoses pathologiques peuvent constituer une complication sérieuse de la thérapie prolongée par des corticostéroïdes exogènes.

Equimosis corticosteroides

SUMARIO

Durante un período de un año, 58 enfermos con artritis reumatoide y con espondilartritis anquilosante,

sometidos a terapéutica de larga duración con corticosteroides, fueron repetidamente examinados para comprobar la presencia o ausencia de equimosis patológicas. De 40 enfermos tratados con corticosteroides exógenos, un 60 por ciento presentó equimosis patológicas, y entre 18 tratados con corticotropina ninguno fué afectado de esta manera.

Las equimosis patológicas en tratamiento a largo plazo con corticoesteroides exógenos pueden ser una complicación seria.

UNIVERSITY OF TORONTO

A new rheumatic diseases unit has been formed within the Department of Medicine in the University of Toronto with Dr. Wallace Graham, F.R.C.P., as Director.

As well as the present divisions at Sunnybrook Veterans Hospital and the Toronto General Hos-

pital, a new thirty-bed long-stay active treatment division has been established at the Queen Elizabeth Hospital, Toronto. It is hoped to expand research facilities in the connective tissue diseases.

Dr. Graham is President of the Pan-American League against Rheumatism.

BOOK REVIEW

Arthritis and Allied Conditions. A Textbook of Rheumatology. Edited by Joseph Lee Hollander. 6th ed., 1960. Pp. 1306. Kimpton, London. (150s.)

The sixth edition of this well-established textbook, originally based on Comroe's "Arthritis", has been largely re-written and nineteen new chapters have been added. The contributors include many of the leading authorities in the sphere of rheumatic diseases in North America and the volume is packed with up-to-date expert views in this field.

Dr. John Lansbury has a new chapter on methods of evaluating rheumatoid arthritis. This is a most important subject in view of the many clinical trials of anti-rheumatic drugs which are now being carried out. The author has given a clear summary of the present position, pointing out many inadequacies in the methods in use at the present time. He gives stimulating ideas for improvement in techniques though the reviewer doubts whether morning stiffness can yet be measured.

Dr. E. P. Engleman has an excellent chapter on the basic treatment of rheumatoid arthritis, pointing out the necessity for systemic, emotional, and articular rest with good advice on analgesics and diet.

Dr. J. J. Bunim has contributed a first-class review of the chemistry, physiology, and metabolic effects of corticosteroids, and has included the new work on the cortisol-binding protein transcortin as well as the latest views on absorption and distribution of steroids and of the metabolic fate and excretion of these substances. This is one of the outstanding chapters in the book. He also has an excellent chapter on the use of synthetic corticosteroids in rheumatoid arthritis, including the clinical considerations, limitations, and adverse effects with most helpful advice on individual steroid preparations.

Dr. Hollander himself, from his large experience, has written most wisely on the value of intra-articular steroid therapy with helpful diagrams and photographs showing methods of injection for various joints. He deals sensibly with the recent reports that "Charcot's arthropathy" may occur after this treatment, pointing out that it is a possibility and that careful radiological supervision is necessary. In his very large series the incidence of this complication is a fraction of 1 per cent.

Dr. Wallace Graham has a wise chapter on the relation-

ship of infection to rheumatoid arthritis, pointing out the absence of any controlled observations as to the validity of this theory; yet, as he says, "As long as the cause of rheumatoid arthritis is unknown, the possible role of as yet unknown infectious agents remains a possibility."

The diffuse connective tissue diseases, systemic lupus erythematosus, polyarteritis, and dermatomyositis are superbly covered by Dr. L. E. Shulman and Dr. Harvey, with clear descriptions of the clinical and pathological features. They point out that the introduction of corticotrophin and cortisone provided the first significant advance in the management of patients with systemic lupus erythematosus, but that the basic disease process is not fundamentally altered by these drugs. They observe that the relationship between polyarteritis and rheumatoid arthritis is not yet clearly understood. They discuss at length the role of peripheral neuritis in polyarteritis and in rheumatoid arthritis treated with steroids and quote the opinion of Sokoloff and Bunim, that "Polyarteritis in rheumatoid arthritis may be interpreted as an exaggerated form of rheumatoid arthritis rather than an independent finding."

There is an excellent chapter on gout and the newer uricosuric agents by Dr. C. J. Smyth, who points out the curious paradoxical effect of salicylates which in small doses raise the serum uric acid level yet in very large doses cause uricosuria.

The one disappointing section of this textbook is that on degenerative joint disease. Admittedly there is not nearly so much clinical or pathological research being undertaken in this field as in rheumatoid arthritis or the diffuse connective tissue diseases, but out of 1,280 pages only about fifty are devoted to the very common condition of osteoarthritis. Phenylbutazone, which is used so widely, is covered in only a few lines of the text.

Dr. Joseph Hollander and his team of contributing editors are to be heartily congratulated on the new edition of this magnificent volume. The book has grown in size owing to the increasing interest of the whole medical profession and to the increasing amount of research which is being carried out. No physician or surgeon with an interest in this large group of common diseases can afford to be without this book.

OSWALD SAVAGE.

BRITISH COUNCIL

The following is a resumé of a paper given by Prof. Nestorov and Dr. Sachkov, of the Academy of Medical Sciences of Moscow, entitled "An Elaboration of a Special Method for the Diagnosis of Rheumatic Fever and the Degree of its Activity".

The most important deficiency of the known methods for the diagnosis of rheumatic fever is their non-specificity.

When considering rheumatic fever and other collagen diseases as auto-immune diseases, in the pathogenesis of which streptococcal infection plays the main part, we

believe that the study of the main antigens and antibodies which participate in the process is most promising.

Changes in the antigenic structure of human protein in the affected organisms are essential for diagnosis, as is partly apparent when examining the antigenic properties of human serum.

In typical cases of rheumatic fever and rheumatoid arthritis, we separated electrophoretically homogeneous fractions of the serum proteins and used them for the immunization of rabbits in order to obtain appropriate antisera.

Antisera for single fractions were studied in cross-experiments with sera of patients with rheumatic fever, rheumatoid arthritis, lupus erythematosus, scleroderma, and other collagen and non-collagen diseases, as well as with sera of perfectly healthy individuals.

Various immunological processes were worked out and used for this purpose as well as certain physicochemical methods, such as di-electrical measurements, immuno-electrophoresis in gel and on paper, gel-precipitation, etc.

The results of our investigations carried out by various methods showed, as a rule, the presence of antigens in the serum of rheumatic fever, rheumatoid arthritis, and of other collagen diseases, which were apparently specific for a given group of diseases.

Apart from the common antigen in blood serum, it is possible, we believe, to determine the antigen which is specific for rheumatic fever.

Accordingly, we propose to apply this method to the specific diagnosis of rheumatic fever and the degree of its activity.

The basis of this method is the reaction of the investigated serum with the diagnostic rabbit antiserum against serum gamma-globulin of rheumatic fever patients by means of immuno-electrophoresis.

There is reason to believe that a further study of the antigenic properties of serum proteins can lead to more differentiated clinico-immunological characteristics of different forms and stages of rheumatic fever and, possibly, to a specific diagnosis of other collagen diseases.

NEW ZEALAND RHEUMATISM ASSOCIATION

Annual Report, 1960

The 13th Annual General Meeting of the New Zealand Rheumatism Association was held at Palmerston North Hospital on October 6-7, 1960. The President, Dr. A. Rowatt Brown, and nineteen members were present. The following officers were elected for the period 1960-62:

<i>President:</i>	Dr. B. S. Rose.
<i>President-Elect:</i>	Dr. F. H. Swan.
<i>Secretary-Treasurer:</i>	Dr. I. C. Isdale, Queen Elizabeth Hospital, Rotorua.
<i>Committee:</i>	Dr. C. Gresson. Dr. Moore Tweed. Dr. J. Valentine. Dr. T. C. Highton. Mr. C. Milsom.
<i>Ex officio:</i>	Dr. A. Rowatt Brown. Prof. E. Sayers.

A programme for 1960-61 was outlined to enlarge the scope of the New Zealand Branch of the Empire Rheumatism Council, and Dr. Wrigley was congratulated on being appointed Empire Rheumatism Council Travelling Fellow for 1960. It was proposed to discuss future appointments with the Australian Rheumatism Council at the B.M.A. Conference in Auckland in 1961.

Dr. C. Gresson reported for the Advisory Committee on Research on the work being done in the Medical School at Dunedin; a vote of thanks to the

Empire Rheumatism Council was passed and a hope expressed that the grant might be continued in the future.

Dr. A. Rowatt Brown took as the subject of his Presidential Address "Rheumatism, A National Problem".

A clinical session of interesting cases was arranged, with a pathological demonstration, and the following papers were given:

DR. T. C. HIGHTON and DR. E. J. WILLIAMSON (*Department of Medicine, University of Otago*): The Influence of Some Nitriles and Some Pyrrolidine Compounds on the Formation of New Collagen.*

DR. I. C. ISDALE and DR. B. S. ROSE: The Vanishing Hip.

DR. R. D. WIGLEY, DR. H. E. HUTCHINGS, and DR. B. P. MACLAURIN: The Relationship of Chronic Ulcerative Colitis to the Rheumatic Disorders.

DR. B. S. ROSE and DR. I. C. ISDALE: Ankylosing Hyperostosis.

MR. DAWSON reviewed a series of cases treated by surgery and presented a short film showing his cures.

MR. CHRISTIE presented a paper on aspects of surgery in rheumatic disease.

DR. I. BROADFOOT gave a paper on electronography in rheumatic disease.

* Our thanks are due to the New Zealand Medical Research Council for paying the salary of T. C. Highton and to the Empire Rheumatism Council for a very generous grant which paid the salary of E. J. Williamson and is paying the expenses of this and related research programmes in this Department.

ABSTRACTS

This section of the ANNALS is published in collaboration with the two abstracting Journals, ABSTRACTS OF WORLD MEDICINE, and OPHTHALMIC LITERATURE, published by the British Medical Association.

The abstracts selected for this Journal are divided into the following sections: *Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects.* At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi of steroid therapy.

Acute Rheumatism

Problems associated with the Use of Antibiotics for the Prevention of Primary Episodes of Rheumatic Fever. SASLAW, M. S., JABLON, J. M., and JENKS, S. A. (1960). *Amer. J. Cardiol.*, 5, 777. 5 refs.

A pilot experiment in the control of streptococcal infection in the community is described in this paper from the National Children's Cardiac Hospital, Miami, Florida. All the children absent because of respiratory illness or fever from a school of 824 pupils aged 6 to 12 years were visited at home; during the 60 school days covered by the investigation there were 375 absences attributed to respiratory illness. A total of 344 throat swabs were collected and cultured; 98 of these yielded β -haemolytic streptococci, 78 of which belonged to Group A. The children were treated by their own doctors, although some received no medical supervision. The authors, when their advice was sought, recommended a single injection of 1.2 million units of "bicillin". They found, however, that most doctors gave penicillin in inadequate dosage or some other antibiotic or sulphonamide, or prescribed no specific treatment at all. The patients were followed-up for 2 weeks to 3½ months, and 29 swabs still yielded Group-A streptococci. Rheumatic fever and glomerulonephritis did not occur in any of the children who had been found to harbour β -haemolytic streptococci.

The authors consider that the cost of a comprehensive plan to eradicate rheumatic fever by the immediate treatment of streptococcal throat infections in school children would be prohibitive. Such a scheme might also encounter difficulties in co-operation from the lay public, and doctors would require education in what constituted adequate treatment of a streptococcal throat infection in a child.

[Some of the difficulties met in this study might have been reduced if the authors had sought the co-operation of the parents and the physicians before starting the experiment.]

Bernard Isaacs.

Group A β -Haemolytic Streptococci and Rheumatic Fever in Miami, Florida: III. Bacteriologic Observations on β -Haemolytic Streptococci Other than Group A. STREITFELD, M. M., and SASLAW, M. S. (1960). *Dis. Chest*, 38, 73. 9 refs.

This paper, one of a series from the University of Miami, Florida, describes a further study of the bacterial flora of the human throat, with special reference to the incidence of β -haemolytic streptococci other than those of Group A. Altogether 11,014 throat swabs from children and adults in Dade County, Miami, were cultured between February, 1953, and May, 1956, and β -haemolytic streptococci other than Group-A organisms were isolated from 7.6 per cent. (Group B, 1.3 per cent.; C, 2.6 per cent.; F, 0.7 per cent.; G, 2.3 per cent.; ungroupable, 0.7 per cent.). No difference was observed between children and adults in the incidence of the different groups of organisms, but positive cultures were obtained twice as often from negro children as from white, the difference being largely due to a sixfold increase in the incidence of Group-C organisms. The authors conclude that the frequency with which β -haemolytic streptococci other than Group-A were isolated emphasizes the need for grouping these organisms when assessing their significance in the diagnosis of rheumatic fever.

Allan St. J. Dixon.

Streptococcal Infections in Adolescents and Adults after Prolonged Freedom from Rheumatic Fever. I. Results of the First Three Years of the Study. JOHNSON, E. E., STOLLERMAN, G. H., GROSSMAN, B. J., and McCULLOCH, H. (1960). *New Engl. J. Med.*, 263, 105. 2 figs, 18 refs.

The incidence and complications of streptococcal infections were studied in 298 adolescents and adults at the La Rabida Jackson Park Sanitarium or the Northwestern University Medical Clinics, Chicago, who had had rheumatic fever and who, as the result of continuous penicillin prophylaxis, had been free from recurrence for at least 5 years. Prophylaxis was stopped and the

patients were examined at least every 2 months, when throat swabs were taken for culture and specimens of serum obtained for determination of the anti-streptolysin-O titre. All patients were examined promptly when an illness was reported. Symptomatic streptococcal infections were treated with a single injection of 1,200,000 units benzathine penicillin intramuscularly. The patients were divided into two groups: 204 adolescents aged 11 to 22 years and 94 adults aged 23 to 70 years.

A total of 115 streptococcal infections occurred over a follow-up period of 572 patient years. These were symptomatic infections in 22 cases (19 per cent. of the total). There was one relapse of rheumatic fever in this group the patient being inadequately treated by the family doctor. Subclinical asymptomatic infections characterized by a rise in streptococcal antibody titre occurred in 74 patients; these comprised 64 per cent. of all infections. In 58 patients in this group cultures of throat swabs were positive. There were six recurrences of rheumatic fever. Of the streptococcal infections nineteen (16 per cent. of all infections) were questionable because they were asymptomatic and not associated with a rise in antibody titre, but characterized only by positive throat culture. There were no rheumatic relapses in this group. A significantly higher incidence of infection was observed in the adolescent group (23.2 per 100 patient years) than in the adults (12.8 per 100 patient years). This was accounted for by a higher incidence of subclinical infection in the adolescents. However, respiratory infections were reported more frequently in the adults. All seven rheumatic recurrences were seen in the adolescents, six after subclinical infections. There was thus a rheumatic recurrence rate of 1.8 per cent. per patient year in adolescents and 9 per cent. per subclinical infection. This contrasts with a recurrence rate of 2.4 per cent. per patient and 17.5 per cent. per subclinical infection in a concomitant study of children receiving prophylaxis. There was therefore a downward trend with age, both in the incidence of haemolytic streptococcal infections and in the frequency which these were followed by rheumatic fever.

C. Bruce Perry.

Prevention of Recurrent Rheumatic Fever in Children and Adults with Oral and Repository Penicillin. MOU, T. W., FELDMAN, H. A., and HARTENSTEIN, H. (1960). *Amer. J. med. Sci.*, **239**, 403. 2 figs, 23 refs.

The authors of this paper from the Departments of Preventive Medicine and Pediatrics, State University of New York, describe their experience at a rheumatic-fever prophylaxis clinic, where during the first 3 years of its existence 139 patients were observed for a total of 1,978 patient-months. The ages of the patients (55 male and 84 female) ranged from 8 to 74 years, only 39 being under 20 years. Once a month throat swabs were taken for culture and blood samples for estimation of the erythrocyte sedimentation rate, the haematocrit and C-reactive protein values, and the antistreptolysin-O titre. Alternate patients were assigned to one of two groups, the first receiving 200,000 units benzathine

benzylpenicillin in tablet form once daily and the second 900,000 units benzathine benzylpenicillin intramuscularly once a month. Patients with a history of penicillin hypersensitivity or who developed such hypersensitivity were given 0.5 g. sulphamethoxypyridazine daily.

No recurrences of acute rheumatic fever were encountered during the period of observation. Discomfort or pain in the joints was reported at some time by 59 (42 per cent.) of the patients—slightly more frequently by those receiving penicillin intramuscularly than by patients given penicillin by mouth. The incidence of sore throat and other upper respiratory tract infections was about the same in the two groups (difference within 1 per cent.). Auscultation of the heart revealed no change during the observation period in 109 patients, fewer murmurs in thirteen patients, and more murmurs in seven; in ten patients the findings by auscultation were unreliable throughout. Group-A streptococci were isolated three times, Group-B streptococci three times, and Group-C streptococci twice. An increase in the antistreptolysin-O titre was noted in 23 patients (thirteen oral penicillin, ten intramuscular), who had failed to receive penicillin for a month or more. Among patients receiving penicillin regularly a significant rise in antistreptolysin-O titre was noted in thirty given intramuscular injections and in 22 given the antibiotic by mouth. When the data on antistreptolysin-O titres for both groups were combined a progressive fall in the median titre was noted during the period of observation, although new patients were added as they were admitted to the clinic. Few allergic reactions were seen, and these were of little consequence apart from one episode of anaphylaxis following an initial injection.

C. E. Quin.

Concept of Egg Yolk as a Dietary Inhibitor to Rheumatic Susceptibility. COBURN, A. F. (1960). *Lancet*, **1**, 867. 23 refs.

It is now accepted that the haemolytic streptococcus is the infective agent in rheumatic fever, but the factors which determine rheumatic susceptibility are uncertain. After the Second World War, in one area in Chicago where there was an increased food consumption associated with a rise in family income, a marked decline in the incidence of rheumatic fever was noted, in spite of the occurrence of the expected number of Group-A streptococcal infections. This fall, however, was not observed among the Negro population in a nearby neighbourhood, whose family incomes remained extremely low.

Analysis of information concerning diet obtained from the replies to a questionnaire suggested the possibility of an association between poverty and low consumption of egg yolks by children in whom rheumatic disease developed. Small groups of rheumatic children were therefore given supplements of egg yolk or fractions of egg yolk in their diet. It was found that the incidence of recurrence of rheumatic fever after streptococcal infection fell below that anticipated. The author states that an anti-allergic component has been isolated from egg yolk; this is an alcohol-soluble substance and protects animals against immediate and delayed types of hypersensitivity.

It is concluded that since the underlying biochemical mechanism of the rheumatic state is not known its relation to nutrition in infancy remains to be determined.

B. M. Ansell.

Pulmonary Veins in Rheumatic Heart Disease. ORMOND, R. S., and POZNANSKI, A. K. (1960). *Radiology*, 74, 542. 12 figs, 16 refs.

The relationship between pulmonary vein size and left atrial pressure was studied at the Henry Ford Hospital, Detroit. Conventional postero-anterior chest radiographs of 172 patients who had undergone cardiac catheterization were examined and the size of the pulmonary veins was graded subjectively on a 1 to 3 scale by different observers. The left atrial pressure had been measured by percutaneous catheterization in 107 of the patients, but was not known when reading the plain radiographs.

A definite correlation was noted between the size of the veins and the pressure, the nature of the valve lesion having no effect. The upper lobe veins were found to be most reliable, the right upper lobe vein being fairly easy to locate where it crosses the right main bronchus. The lower lobe veins were disproportionately enlarged in the presence of congestive failure.

D. E. Fletcher.

Comparison of the Effect of Prednisone and Acetylsalicylic Acid on the Incidence of Residual Rheumatic Heart Disease. COMBINED RHEUMATIC FEVER STUDY GROUP (1960). *New Engl. J. Med.*, 262, 895. 11 refs.

Of the eight hospitals which took part in the Combined Rheumatic Fever Study Group set up in 1956 to compare the effects of prednisone and aspirin in the treatment of rheumatic heart disease in children, four were in New York City, two in Baltimore, one in Boston, and one in Cleveland, Ohio. In this paper the investigators report on the results of a carefully controlled study of 57 patients who were all aged 12 years or under and in whom the attack of rheumatic carditis was the first one and had not been present for more than 28 days. The other stringent criteria for admission to the trial were the presence of one or more of the following signs: a pericardial friction rub or effusion, unequivocal cardiac enlargement confirmed radiographically, congestive cardiac failure, and a significant aortic or apical diastolic murmur or a Grade-3 apical systolic murmur; a Grade-2 apical systolic murmur was accepted only if a diastolic murmur or other stigmata of carditis were present. Patients were assigned to one of two treatment groups by random selection: Group 1 received prednisone in a dosage of 60 mg. daily for 3 weeks in divided doses, this being then gradually reduced over the subsequent 9 weeks until a total of 3 g. had been given; Group 2 was given acetylsalicylic acid in a dosage of 50 mg. per lb. (110 mg. per kg.) body weight daily in divided doses for 9 weeks, followed by 30 mg. per lb. (66 mg. per kg.) daily in divided doses for 2 weeks and then 15 mg. per lb. (33 mg. per kg.) daily for one week, this dosage being aimed at maintaining a serum salicylate level of between 25 and 35 mg. per 100 ml. For the eradication

of Group-A streptococci both treatment groups received penicillin in doses sufficient to maintain therapeutic levels for 10 days and this was followed by long-term prophylaxis with one of the currently accepted prophylactic regimens. For the purposes of the trial the clinical and laboratory findings in each patient were recorded on admission, then after 12 weeks' therapy plus 3 weeks' observation, and finally one year after the completion of the therapy and observation periods.

Both prednisone and salicylates suppressed the inflammatory reaction caused by acute rheumatism, but no superiority was found in the group receiving prednisone as compared with that receiving salicylates. Even though clinical and other objective manifestations of the acute disease were well controlled, cardiac damage was not prevented. Although none of the 28 patients receiving these large doses of prednisone suffered any serious untoward reaction, the investigators consider that in view of the lack of significant reduction in residual heart damage such high dosage of steroids is unwarranted.

J. Warwick Buckler.

Histopathology of Cerebral Rheumatism. [In Russian.] ČALISOVA, K. N. (1960). *Z. Nevropat. Psihiat.*, 60, No. 3, 269. 4 figs, 8 refs.

This communication reports a series of sixteen cases of cardiovascular rheumatism in which lesions of the brain developed, usually as a sequel to diffuse thrombovasculitis. One case is described in detail.

A woman of 33 who had suffered from rheumatism from childhood and had had recurrent attacks of carditis, developed a sudden paralysis of the right arm and leg, with nuclear paralysis of the left facial nerve. This cleared up in 4 days, but 2 months later she developed right hemiplegia and aphasia, with pseudobulbar symptoms. This again remitted, but after 7 months the bulbar symptoms recurred, with severe headache, vomiting, and at times loss of consciousness. On admission to hospital she was febrile and the erythrocyte sedimentation rate was 38 mm. in one hour. There were signs of mitral disease and congestive cardiac failure; the blood pressure was 105/70 mm. Hg. Left laryngeal paralysis was present and she had a right hemiplegia. She did not respond to treatment and died a month after admission.

At necropsy the diagnosis of mitral valvular disease was confirmed and in addition the myocardium showed numerous foci of fibrosis. There were multiple haemorrhagic infarcts of the lungs and kidneys. The cerebral hemispheres showed large areas of softening with cyst formation. The vessels of the cerebral cortex, cerebellum, subcortical ganglia, pons, and medulla showed advanced vasculitis with thickening and often calcification of the walls, narrowing of the lumen, and hyalinization of the muscular coat; the collagen fibres were swollen and stained poorly. In some areas there was oedema of the perivascular spaces. Diffuse proliferation of the glia was observed. Thus in this case the brain symptoms resulted, not from embolism, but from a diffuse vascular disease of rheumatic nature.

L. Firman-Edwards.

Masuda's Retinitis in a Patient with Rheumatic Endocarditis. (Su un caso di retinite di Masuda in soggetto con esiti di endocardite reumatica.) SANTINO, D. (1959). *G. ital. Oftal.*, **12**, 401. 2 figs, 15 refs.

The author discusses the frequency of concomitant rheumatic disease in exudative central retinitis and suggests that the changes in the choroidal capillaries (similar to those seen in other organs in rheumatic subjects) are the cause of the retinitis. *M. H. T. Yuille.*

Acute Benign Pericarditis and Acute Articular Rheumatism in Children. (Péricardite aiguë bénigne et rhumatisme articulaire aigu chez l'enfant.) MARQUEZY, R. A., and BACH, C. (1960). *Sem. Hôp. Paris*, **36**, 1206. 16 refs.

Acute benign pericarditis in adults is not uncommon but in children appears to be rare, the authors having found only 29 cases reported in the literature. In this paper they describe three cases of pericarditis in children, not due to rheumatism, seen at the Hôpital Trousseau, Paris, between 1948 and 1957, and contrast the findings with those in a similar case of rheumatic origin.

The first patient was a boy of 13 who had six separate attacks of pericarditis in one year, the signs being pain, fever, and pericardial friction; on each occasion these responded to administration of steroids but later recurred. There was no acute joint involvement or cardiac valvular lesion during the year of illness nor in 3½ years of follow-up. The second patient, a boy aged 7, had a single attack of pericarditis associated with a pulmonary infection which responded to penicillin. The third, a boy aged 11, had a single attack of pericarditis with shoulder pain which responded to ACTH; no recurrence and no cardiac lesion was found in 5 years of follow-up. No specific cause was found in any of these three cases, and their subsequent course appeared to exclude rheumatism.

The contrasting case was in a girl aged 13 who had seven attacks of pericarditis in one year, these responding to steroids each time but relapsing after cessation of treatment. From the start she had a pansystolic murmur, and the fifth attack of pericarditis was associated with joint symptoms, making the clinical diagnosis of rheumatism probable. Nevertheless the heart murmur subsequently disappeared, leaving her with an apparently normal heart. *J. A. Cosh.*

Contribution to the Study of Acute Articular Rheumatism in the Adult. (Contribution à l'étude du rhumatisme articulaire aigu de l'adulte.) ABLARD, G., LARCAN, A., GILGENKRANTZ, J.-M., and WELFRINGER, A. (1960). *Rev. Rhum.*, **27**, 191. Bibl.

Young men with known cardiac lesions are naturally excluded from military service, but nevertheless acute rheumatic fever accounts for 5 per cent. of admissions to military hospitals. Between 1951 and 1957 at Metz the authors have observed 352 such cases. It appeared that intense physical effort in untrained men leading a collective existence was an important causative factor. Of 349 of the patients, 220 were suffering from a primary attack and 129 had recurrences. A sore throat preceded the attack by 1 to 30 (mean 13) days, and the lower limbs (mainly the knees) were initially affected in 73·6 per cent.

of cases. The larger joints were usually involved. Nephritis was noted in 2·5 per cent. of cases, but had a favourable outcome.

Cardiac damage was not a common occurrence in the adult; thus among the last 152 patients seen only four complained of precordial pain, three of palpitations, and one of dyspnoea. In eight cases cardiac arrhythmia was confirmed by the electrocardiogram (ECG), while in eighteen there was a pericarditis (with effusion in three). About one-quarter of all patients had a cardiac murmur on admission; systolic murmurs usually disappeared but diastolic murmurs tended to persist. Definite valvular lesions were noted in 12·7 per cent.; of these, 50 per cent. were purely mitral, 30 per cent. aortic, and 20 per cent. combined. The lesion was usually one of regurgitation [stenosis would take time to develop]. Abnormal ECG findings were often transitory; inverted T-waves associated with pericarditis were noted in 3·3 per cent. and lengthening of the P-R interval in 22·5 per cent.

While myocarditis and pericarditis reacted well to treatment with salicylates, phenylbutazone, and hormones, the effect on endocarditis was uncertain. The authors discuss the criteria for the diagnosis of acute rheumatic fever and emphasize the desirability of differentiating the condition from streptococcal throat infections in which more permanent articular damage may occur. *D. Preiskel.*

Prophylaxis of Rheumatism with "Iversal". (Rheumatismus-prophylaxe mit Iversal.) LORENZ, K. (1960). *Mschr. Kinderheilk.*, **108**, 268. 11 refs.

Because side-effects are apt to occur during continuous prophylaxis with both sulphonamides and penicillin in children who have had an attack of rheumatic fever, other forms of chemoprophylaxis may be tried. For this purpose the author, working at the Children's Hospital, Dresden, has used "iversal", a compound synthesized in 1955 by Domagk and Petersen, of which the chemical composition is benzochinon-guanylhydrazon-thiosemicarbazone. It is highly effective locally against streptococci in dilutions of up to 1 : 10⁶, but even this concentration cannot be obtained in the bloodstream after systemic administration without causing toxic side-effects. The drug is normally dispensed in chocolate-flavoured tablets containing 10 mg. of the active substance, these being given four or five times daily and allowed to disintegrate slowly in the mouth—they must not be chewed or swallowed. Used in this way they cause no toxic side-effects and are well tolerated by children for a short time, but after some weeks the taste becomes unpalatable and there is also a definite loss of appetite. The author found that better tolerance was achieved when the tablets were flavoured with peppermint.

Altogether 45 rheumatic children have been treated for a total of 16 patient-years [that is, the average duration was only about 4 months] and during this time no recurrences of rheumatic fever were observed. Nevertheless, haemolytic streptococci were recovered on throat swabbing from ten children on seventeen occasions. There was no concurrent sore throat or a rise in the anti-

streptolysin-O titre. These children were considered to be carriers of the streptococci. Prophylaxis with iversal is thought to be particularly valuable in children who are sensitive to penicillin.

John Lorber.

Effect of Antiserotonin on Rheumatic Fever. (Azione di una antiserotonina sulla flogosi reumatica.) GARELLI, R. (1960). *Reumatismo*, 12, 92. 6 refs.

Streptolysin Test in the Diagnosis of Rheumatic Fever. (Der Streptolysin-Intracutan-Test in der Diagnostik der Febris rheumatica.) DONÁTH, I. (1960). *Z. Rheumaforsch.*, 19, 355. 1 ref.

Acute Infectious Rheumatism due to Streptobacillar Sepsis. LOSANDA L., M., ROESCHMANN, W., and DÍAZ C., E. (1960). *Arch. interamer. Rheum.*, 3, 206. 6 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Results of Rehabilitation and Resettlement in Rheumatoid Arthritis. HARRIS, R. (1960). *Ann. phys. Med.*, 5, 194. 6 refs.

During the 5-year period 1953-58, of the 1,928 patients admitted for treatment to the rehabilitation unit of the Devonshire Royal Hospital, Buxton, Derbyshire, nearly half (988) had rheumatoid arthritis. There was a preponderance of females in the ratio of 1.9 : 1, as compared with 1.4 : 1 for all admissions, and 59% of the patients were in the age group 40 to 60 years. Although the disease was chronic in the majority of these patients severe disability was of relatively recent origin.

At the time of admission to the unit 55 per cent. of the patients showed considerable disablement, but on discharge only 25 per cent. did so. The corresponding figures for those who were regarded as being "fit for any work" were 14 and 51 per cent. respectively. In 69 per cent. of cases the duration of in-patient treatment at the unit was less than 3 months. When it was considered that a change of occupation was indicated the cases were discussed at a resettlement clinic attended by, among others, a disablement resettlement officer, an almoner, and a member of the medical staff with special experience in industrial medicine. Follow-up observations were maintained for 2 to 3 years after discharge, and showed that more than half the subjects had remained in steady employment. Resettlement as skilled clerical workers was achieved by most of the women who had been so employed before their illness. On the other hand, male workers employed in heavy industry usually returned to less skilled employment; for instance, one former worker at the coal face became a surface-haulage hand. Only 20 per cent. of the men were placed in skilled jobs, as compared with 52 per cent. initially in such jobs. Nevertheless, the results compare favourably with those obtained by other investigators, for almost all those who had been placed at work within 3 months of discharge from hospital were still in employment 2 to 3 years later.

A. Garland.

Rheumatoid Arthritis and Polyneuritis. (Polyarthrite rhumatoïde et multinévrite.) COSTE, F., DELBARRE, F., and BASSET, F. (1960). *Rev. Rhum.*, 27, 169. 10 figs.

The authors point out that in their recent review, with Cayla (*Presse méd.*, 1959, 67, 1177; *Abstr. Wld Med.*, 1960, 27, 55) of 100 cases of rheumatoid arthritis treated for long periods with adrenocortical hormones it chanced that no case of polyneuritis occurred. However, they now comment on the increasing incidence of this complication and cite reports by various French workers, and in particular that by Johnson and others (*Arthr. and Rheum.*, 1959, 2, 224; *Abstr. Wld Med.*, 1960, 27, 56) who described seventeen cases, three in detail. In this paper from the Hôpital Cochin, Paris, they discuss the relationship between rheumatoid arthritis and periarteritis nodosa and describe three patients with long-standing rheumatic disease who developed signs suggesting involvement of several peripheral nerves and in each of whom biopsy specimens showed the histological appearances of periarteritis nodosa. In the first case the periarteritis appeared quite suddenly after several years of steroid therapy in rather high dosage. In the second, it occurred on the abrupt withdrawal of corticotrophin (ACTH), and in the third, polyneuritis appeared in a patient who had previously exhibited toxic reactions to a variety of drugs. The change in the clinical picture, therefore, appeared to be related to the therapy. In two patients the condition markedly deteriorated and they subsequently died.

The authors conclude that although it is hazardous to discuss the relationship between rheumatoid disease and periarteritis nodosa, since the aetiology of both is so obscure, they consider nevertheless that periarteritis nodosa is a separate entity and suggest that it may occur in association with rheumatoid disease because the vascular changes which take place in the latter condition offer a milieu suitable for its appearance.

B. E. W. Mace.

Rheumatoid Neuropathy. HART, F. D., and GOLDING, J. R. (1960). *Brit. med. J.*, 1, 1594. 25 refs.

Writing from Westminster Hospital, London, the authors discuss 42 cases of rheumatoid neuropathy as seen in eighteen men and 24 women ranging in age from 36 to 88 years, the majority being aged between 40 and 60. In fifteen of these cases no steroids had been administered within 3 years of the onset of the neuropathy, and twelve had received no steroids at all. A further twenty, however, had regularly received steroids and in six there had been a recent sudden withdrawal of this treatment.

In thirteen cases the onset of the condition was abrupt, with numbness and "deadness" in the toes and feet or intolerable burning pain, but in the others it was more gradual and insidious. The complaint was usually bilateral and symmetrical. Sensory changes were considerable and affected all modalities, but sense of position usually remained well preserved. Although there was muscle wasting and loss of power in many cases, in only eight was the ankle reflex absent bilaterally. In two cases there was transient facial hypo-aesthesia at the time of development of the neuropathy. The presence of L.E.

cells was established in only four patients. The serum vitamin B₁₂ level was found to be normal in the nine cases in which it was assayed. In regard to outcome, of the 42 cases twenty have remained unchanged, fourteen have improved, two patients have died, five have apparently recovered, and one runs a fluctuating course. No treatment seems to be effective. Vascular necrotic lesions of the fingers occurring during the course of this condition constitute a bad prognostic sign. In five patients examined at necropsy, in all of whom "steroid therapy clearly contributed to the general condition and downhill course", diffuse arteriopathy with arteritis of the vasa nervorum was found and this, at least at present, is generally accepted as the probable explanation of the condition, though it does not explain adequately all cases.

G. S. Crockett.

Neuropathy in Rheumatoid Disease. STEINBERG, V. L. (1960). *Brit. med. J.*, **1**, 1600. 19 refs.

From the London Hospital are described eighteen cases in which neurological lesions occurred during the course of rheumatoid arthritis. Although the condition seems to have been originally described by French workers in 1887, there has recently been an increase in the number of these cases, perhaps coinciding with the introduction of steroid therapy. The condition is equally distributed between the sexes, although rheumatoid arthritis is at least twice as common in women as in men. Of the present series five patients died, all within a year of onset of this complication, three of them within one month. It must thus be considered to carry a serious prognosis.

The lower limbs only were involved in twelve cases, the arms only in one, and both upper and lower limbs in five. The symptoms were mainly a sensation of tingling, burning, and numbness of the extremities, but muscle pain was also often present with tenderness of the calves; in all cases objective sensory loss to light touch, pinprick, and temperature was found. The deep reflexes were generally preserved, except for the ankle jerks in seven cases. There was motor weakness in some cases, accompanied by foot-drop in six. In ten of the cases there appeared to be some connexion between the onset of this complication and steroid therapy which had either just been started, or recently stopped, or the dosage of steroids drastically reduced. The complication was not affected by any form of treatment. L.E. cells had been detected in the serum of three male patients at one time or another. There was *post-mortem* evidence of arteritis in the peripheral nerves in two cases, and it is considered that this may be the cause of the neuropathy.

G. S. Crockett.

Scleromalacia Perforans as a Complication of Rheumatoid Arthritis. WILLIAMS, G. T., and ROSENTHAL, J. W. (1959). *Ann. intern. Med.*, **51**, 801.

Anaemia of Rheumatoid Arthritis in Children. (Die Anämie bei rheumatoider Arthritis im Kindesalter.) KÖLLE, G., and STOEGER, E. (1960). *Z. Rheumaforsch.*, **19**, 331. 1 fig., bibl.

Septic Arthritis of the Knee. (Artritis septica de rodilla.) GARIULO, H. E., and CONCILIO, A. (1960). *Rev. argent. Reum.*, **25**, 250.

Pulmonary Complications in Rheumatoid Arthritis. (Les pneumopathies de la polyarthrite chronique évolutive.) BONARD, E. C., and VASEY, H. (1960). *Schweiz. med. Wschr.*, **90**, 866. 5 figs, 47 refs.

Position of Rheumatoid Arthritis in the Classification of the "Rheumatic" Diseases. (Die chronisch-rheumatoide Polyarthritits und ihre Stellung im Rahmen der rheumatisch genannten Erkrankungen.) THURNER, J. (1960). *Z. Rheumaforsch.*, **20**, 373. 12 figs, 74 refs.

Arteritis in Rheumatoid Arthritis. ARONOFF, A., JOHNSON, L., and DWORKIN, S. (1960). *Canad. med. Ass. J.*, **83**, 58. 8 figs, 17 refs.

Gastric Function and Phosphocalcium Imbalance in Rheumatoid Arthritis. (Fonction gastrique et déséquilibre phosphocalcique au cours de la PCE.) LOUYOT, P., GAUCHER, A., METZ, R., and GOULON, Mme. (1960). *J. belge Méd. phys. Rhum.*, **15**, 135. 8 figs.

Method of Evaluating Drugs in the Treatment of Rheumatoid Arthritis. Phenylbutazone, Oxyphenylbutazone, Cortisone, and Prednisone. (Método de valoración de drogas en la artritis reumatoidea. Valores obtenidos con la fenilbutazona, oxifenilbutazona, cortisona y prednisona.) SMYTH, C. J. (1960). *Arch. argent. Reum.*, **23**, 54. 3 figs, 10 refs.

(Osteo-Arthritis)

Correction of the Position of the Hip in Severe Osteo-Arthritis. (La réposition de la hanche dans les coxarthroses sévères.) FORESTIER, J., CERTONCINY, A., and FORESTIER, F. (1960). *Rev. Rhum.*, **27**, 186. 3 figs.

Osteo-arthritis of the hip-joint remains a serious problem in view of the disappointing long-term results of the Smith Petersen and Judet type of operation, to which most of the authors' cases have been subjected at Aix-les-Bains since 1945. They have therefore reviewed some forty of their earlier cases which were treated by non-operative repositioning of the hip under general anaesthesia, and now describe the technique employed and the results obtained in 22 of these patients, aged 33 to 74 years, who were treated between 1938 and 1946 and were available for follow-up after 13 to 20 years.

Their method of repositioning is as follows: Under general anaesthesia the hip-joint is put through a maximum range of movement, this resulting in capsular and ligamentous tears which subsequently cicatrize and help to fix the joint. The hip is then placed in the "physiological" position and the pelvis and the lower limbs encased in plaster reaching down to the ankle on the treated side and to the knee on the opposite side. After 18 to 20 days the cast is sectioned and the patient gradually mobilized. The plaster can be discarded after

30 to 40 days, when it is immediately replaced by a special leather or plastic corset which must be worn day and night for 3 months. Later, it may be left off at night, but daytime use is continued for 6 months to 2 years. In these 22 patients the long-term results were gratifying. In most cases pain at rest rapidly disappeared and weight-bearing was tolerated. The limp usually disappeared, but was replaced by claudication due to joint stiffness; this, however, gradually improved. Radiologically, improvement was evident in the reappearance of the joint outline and improved bone texture of the head of the femur and acetabulum. It is claimed that this "medical arthrodesis" is better tolerated by the elderly patient than surgical intervention, and that the latter can always be kept in reserve, but in most cases will probably not be required.

D. Preiskel.

Intra-articular Injections for Osteo-Arthritis. BONNER, C. D. (1960). *Rheumatism*, 16, 84. 1 fig., 12 refs.

Osteo-Arthritis. (Osteoarthritis.) STECHER, R. M. (1960). *Arch. argent. Reum.*, 23, 43. 18 refs.

Sequelae in the Adult of Osteo-chondritis of the Hip in Early Childhood. (Conséquences chez l'adulte de l'ostéochondrite infantile de la hanche.) BLOCH-MICHEL, H., BENOIST, M., SALOMON, A., DURIEZ, J., MOREL, G., and HERIPRET, G. (1960). *Rhumatologie*, 12, 170. 16 figs, 39 refs.

(Spondylitis)

Iridocyclitis in Ankylosing Spondylitis. [In Russian.] SAIKOVA, M. V. (1960). *Vestn. Oftal.*, No. 2, 15. 3 refs.

Manifestations of iridocyclitis and iritis were observed in 7 per cent. of 200 cases of ankylosing spondylitis. Eye involvement was noted in some cases before the joint disease, whereas in others the onset was simultaneous, or the spondylitis preceded the iritis by a few months. Recurrences in both conditions often coincided. The author could find no reference in the literature to ankylosing spondylitis as a cause of iridocyclitis.

A. Swan.

Adaptation to Marie-Strümpell Arthritis. FOWLKS, E. W., BRIDGES, J. A., and HOPKINS, D. (1960). *Arch. phys. Med.*, 41, 516.

Spondylarthrititis Ankylopoietica associated with Iritis. LAITINEN, H., PELTOLA, P., and SARAJAS-KYLLONEN, S. (1959). *Ann. Med. intern. Fenn.*, 48, 87.

Ochronosis: Report of a Case. DI FIORE, J. A. (1960). *Arthr. and Rheum.*, 3, 359. 8 figs, 3 refs.

Ochronotic Spondylitis—Report of Two Cases. NOGUEIRA, A., JR., and BONOMO, I. (1960). *Arch. interamer. Rheum.*, 3, 248. 5 figs, 29 refs.

Carbohydrate Metabolism in Hyperostotic Spinal Arthritis. (Ricerche sul metabolismo degli idrati di carbonio nei malati affetti da atrofi vertebrale a carattere iperostotante.) EINAUDI, G., and VIARA, M. (1960). *Reumatismo*, 12, 163. Bibl.

Pathology of the Peripheral Ligaments of the Lumbar Spine. (Aspectos de la patología del ligamento vertebro-lumbar periférico.) LUCHERINI, T., and LONGO, C. (1960). *Rev. argent. Reum.*, 25, 196. 42 refs.

Lungs in Rheumatoid Spondylitis. TRAVIS, D. M., COOK, C. D., JULIAN, D. G., CRUMP, C. H., HELLIESEN, P., ROBIN, E. D., BAYLES, T. B., and BURWELL, C. S. (1960). *Amer. J. Med.*, 29, 623. 30 refs.

(Miscellaneous)

Radiological and Clinical Investigation of the Temporo-maxillary Joint. Application to the Study of Temporo-maxillary Arthritis in the Course of Chronic Inflammatory Rheumatism (Rheumatoid Arthritis and Ankylosing Spondylitis). (Exploration radioclinique de l'articulation temporo-maxillaire. Application à l'étude des arthrites temporo-maxillaires au cours des rhumatismes inflammatoires chroniques (polyarthrite chronique évolutive et spondylarthrite ankylosante).) MÉRIEL, P., RUFFIÉ, R., CADENAT, H., FOURNIÉ, A., and BLANC, P. (1960). *J. Radiol. Electrol.*, 41, 105. 24 figs, 20 refs.

Writing from the Centre de Rhumatologie, Toulouse, the authors first describe the anatomy of the temporo-mandibular joint, recalling that the condyle of the mandible has two convex surfaces separated by a crest. The whole condyle is intra-articular, but only the anterior aspect is covered with cartilage. The joint, which is a very complex structure, is in relation with the external auditory canal behind and with the chorda tympani, auriculo-temporal nerve, and sympathetic fibres. A biconcave meniscus articulates with the convex upper surface of the mandibular condyle below and the temporal condyle of the zygoma above, thus in effect dividing the joint into two synovial cavities. The movement of the joint is also complicated. In opening the mouth there is first a very slight rotation of the mandibular condyle about its transverse axis and then a forward and downward movement of the temporal condyle; the structure of the joint also allows for free lateral and antero-posterior movements. The articulation of the lower jaw is based partly on the temporo-mandibular joint, but also partly on the articulation with the maxilla along the line of dental closure.

In chronic rheumatism involvement of the joint may give rise to pain in the region of the ear. This pain, which is worst in the morning when the subject first moves his lower jaw, may be unilateral or bilateral and is aggravated by use of the joint in speaking, mastication, or swallowing; indeed the limitation in movement of the

mandible and the desire to avoid the pain may eventually interfere with nutrition. Since the joint is overshadowed by the dense bone formations of the skull, radiology is difficult and requires careful interpretation. The radiograph is taken in profile by siting the x-ray tube at the sigmoid notch of the opposite mandible with the mouth widely open and the cassette parallel to the sagittal plane in contact with the ear on the affected side. The principal rays will therefore be directed upwards and slightly backwards. An antero-posterior exposure is obtained by placing the tube as near the upper and outer angle of the orbit as possible with the mouth open and with the cassette behind the skull, perpendicular to the incident rays. (The method is portrayed in diagrams.) A total of forty cases, comprising 35 cases of adult and five of juvenile rheumatoid arthritis, were studied by the authors. In 21 cases (52 per cent.) there were some subjective symptoms and fourteen had some limitation of movement at the joint, while clinical signs of involvement of the temporo-mandibular joint were noted in 33 (82 per cent.) of cases. Radiology revealed lesions in 37 per cent. and in 27 per cent. there were both clinical and radiological signs. Lesions of the mandibular condyle included erosions of varying extent and depth, cyst formation, osteosclerosis, and atrophy, while calcification of the meniscus was demonstrated in two cases. In one case of juvenile rheumatoid arthritis agenesis of the mandibular condyle and a persistent concavity of the lower border of the mandible were discovered.

Discussing the aims of treatment the authors stress the importance of securing good occlusion in the dental articulation and point out that for this free movement at the joint is necessary. In acute exacerbations they recommend resting of the joint, together with a liquid diet and enforced silence. For local treatment they advocate injections of hydrocortisone.

William Hughes.

Surface Manifestations of Reiter's Disease in the Male.

HANCOCK, J. A. H. (1960). *Brit. J. vener. Dis.*, 36, 36. 13 figs, 4 refs.

A detailed study is reported of the surface manifestations in 76 cases of Reiter's disease in males seen at the Whitechapel [Venereal Diseases] Clinic of the London Hospital. It is pointed out that the clinical material was partly selected in that some of the more severely ill patients were referred for forms of treatment which were not at that time available elsewhere. Involvement of the eyes was encountered in 45 per cent., conjunctivitis being present in 37 per cent., and anterior uveitis in 8 per cent.; balanitis circinata was observed in 26 per cent., lesions of the buccal cavity in 10 per cent., and keratoderma blennorrhagica in 7.8 per cent. The vesicular and erythematous lesions of the tongue and buccal cavity are described in detail [with some excellent colour plates] as are also the lesions of keratoderma and balanitis. All but two patients in the series (with non-gonococcal urethritis, buccal lesions, and keratoderma) exhibited arthritis.

R. R. Willcox.

Recurrent Attacks in Reiter's Disease.

CSONKA, G. W. (1960). *Arthr. and Rheum.*, 3, 164. 1 fig.

The author studied 144 patients with Reiter's disease attending St. Mary's Hospital, London. 88 patients had more than one attack, and there was about the same (14.5 per cent.) risk of a recurrence at any time after the first attack. One patient suffered a relapse after 36 years. When eye lesions were present with the first attack they were markedly more likely to occur in relapses.

W. E. S. Bain.

Aetiology of Non-gonococcal Urethritis and Reiter's Disease.

CSONKA, G. W., and FURNESS, G. (1960). *Brit. J. vener. Dis.*, 36, 181. 16 refs.

An investigation of twenty cases.

P. D. Trevor-Roper.

Case of Reiter's Disease.

[In Polish.] KOZŁOWSKI, J., and ZABIELLO, E. (1959). *Przegl. Derm. Wener.*, 46, 559. 2 figs, 16 refs.

The authors discuss a case of Reiter's syndrome observed during recurrences. Besides the classical triad of symptoms, lesions of the skin and oral mucosa were seen. Electrocardiography showed irregularities. Treatment with antibiotics gave no improvement.

W. H. Melanowski.

Urethro-Oculo-Synovial Syndrome and its Treatment.

[In Russian.] ILYIN, I. I. (1959). *Sovetsk. Med.*, 23, 51.

Extracts from the case histories of four young men observed by the author are presented. The infection was apparently contracted by sexual intercourse. The first symptom of the disease was urethritis, appearing 5 to 16 days after intercourse. Lesions of the joints in three patients preceded conjunctivitis and in one patient conjunctivitis preceded polyarthritis. Reopyrin given in two instances removed the pain.

From an analysis of the literature and personal observation, the author suggests that the formation in the prostate of an inflammatory focus, which upholds the hyperergic state of the organism, initiates the urethro-oculo-synovial syndrome, which is one of the possible complications observed in affections of the prostate. The importance of urological examination for the detection and elimination of the uro-genital focus of inflammation is emphasized.

A. V. Roslavtsev.

Atypical Ocular Manifestations in Chronic Rheumatism.

(Manifestations oculaires atypiques au cours du rhumatisme chronique.) AMALRIC, P., and BESSOU, P. (1959). *Bull. Soc. Ophthal. Fr.*, No. 11, 765. 2 figs.

The author reports some cases of band-shaped keratitis, uveitis, and nodular scleritis associated with polyarthritis.

J. Rougier.

Choline Salicylate: a New, Effective, and Well-tolerated Analgesic, Anti-inflammatory, and Antipyretic Agent.

BRÖH-KAHN, R. H. (1960). *Int. Rec. Med.*, 173, 217. 4 figs, 30 refs.

Observations on the Usefulness of a New Liquid Salicylate in Arthritis. NEVINNY, D., and GOWANS, J. D. C. (1960). *Int. Rec. Med.*, 173, 242. 14 refs.

Comparative Evaluation of the Effectiveness of Choline Salicylate in Treatment of Arthritis and Allied Conditions. THOMAS, R. P., JR. (1960). *Int. Rec. Med.*, 173, 248. 10 refs.

These three papers form part of an American symposium on a new and highly soluble salicylate preparation, the choline salt of salicylic acid ("arthropan"), which appears to represent an advance over previous forms of salicylate therapy. This new agent is given in liquid form in a cherry-flavoured vehicle in a dose of one to two teaspoonfuls (5 to 10 ml.), each teaspoonful containing 870 mg. choline salicylate, that is, the equivalent of 500 mg. salicylate or 10 gr. (650 mg.) aspirin. Tests showed that it is absorbed about five times more rapidly than aspirin and provides peak plasma salicylate levels within 10 minutes, as compared with 120 minutes for aspirin; also several doses may be given each day. All three papers comment on the effective analgesic, anti-inflammatory, and antipyretic actions of the new preparation, on its ease of administration, on the relative lack of gastro-intestinal irritation, and on the fact that patients who cannot tolerate aspirin are able to take choline salicylate.

The author of the first paper, from New York City Department of Health, supervised a long-term co-operative trial of the drug carried out by eighty physicians on 1,200 patients, in many of whom cross-over studies were performed in order to compare it with aspirin. The authors of the second paper, who report from Tufts University School of Medicine, Boston, gave the drug to patients with rheumatoid arthritis, twenty being treated on a short-term basis and thirty receiving long-term maintenance therapy. The third paper, from the Nix Memorial Hospital San Antonio, Texas, also describes the treatment of 45 patients with arthritis. The authors are unanimous in concluding that choline salicylate is a salicylate of choice for all patients with chronic arthritis and the salicylate of choice for the many who are intolerant of other forms of salicylate.

T. B. Begg.

Reiter's Disease. BARON, J. H. (1960). *Brit. J. clin. Pract.*, 14, 679. 9 figs.

Urethro-Conjunctivo-Synovial Syndrome (Reiter's Syndrome). [In French.] PANACCIO, V. (1959). *Urol. int. (Basel)*, 9, 234.

Recurrent Attacks in Reiter's Disease. CSONKA, G. W. (1959). *Urol. int. (Basel)*, 9, 239.

Reiter's Syndrome. (Le syndrome de Reiter.) CAMUS, J. P. (1959). *Maroc méd.*, 38, 1408. 13 refs.

Reiter's Syndrome (Asteromycosis). [In Russian.] VASILEVSKY, M. E., and RZHEVSKY, A. V. (1959). *Klin. Med. (Mosk.)*, 37, No. 5, 142.

Rheumatic Temporal Styloiditis. (Les styloïdites temporales rhumatismales.) LAYANI, F., DURUPT, L., and NADAUD, M. (1960). *Rev. Rhum.*, 27, 387. 6 figs, 3 refs.

Recognition of Intermittent Hydroarthrosis. (Ein Beitrag zur Kenntnis des Hydrops intermittens.) DÜRRIGL, T., and JURAK, H. (1960). *Z. Rheumaforsch.*, 20, 401. 5 figs, 14 refs.

Bechterew's Arthritis. BÖNI, A. (1960). *Arch. interamer. Rheum.*, 3, 385. 5 figs, 13 refs.

Chronic Uro-polyarthritis in the Male. OLHAGEN, B. (1960). *Acta med. scand.*, 168, 339. 16 refs.

Sternoclavicular Arthritis. CRYMBLE, B., and THOMPSON, M. (1960). *Lancet*, 2, 373. 12 refs, 1 fig.

Spondylarthritis and Rheumatoid Arthritis. (Spondylarthritis ankylosante et polyarthrite chronique évolutive.) FORESTIER, J. (1960). *Schweiz. med. Wschr.*, 90, 880. 8 refs.

Present Status of Physical Medicine and Rehabilitation in Treatment of Arthritis. WATKINS, A. L. (1960). *Rheumatism*, 16, 62. 8 refs.

Sex Incidence of Gonococcal Arthritis. GRABER, W. J., III, SANFORD, J. P., and ZIFF, M. (1960). *Arthr. and Rheum.*, 3, 309. 13 refs.

(Disk Syndrome)

Observations on Subluxation of the Cervical Vertebrae in Rheumatoid Polyarthritis. COSTE, F., DELBARRE, F., CAYLA, J., and LAMBERT, P. (1960). *Sem. Hôp. (Paris)*, 36, 1121. 16 figs, 17 refs.

Five case reports are presented (from the Hôpital Cochin, Paris). The first patient, a man aged 53, had severe active rheumatoid arthritis with nodules and a positive sheep cell agglutination test, and required treatment with prednisone. In the fourth year of his disease he developed tenderness and pain of increasing severity in the left suboccipital region. Movements of the head, especially rotation to the left, were painfully restricted. An antero-posterior tomogram showed destruction of the left atlanto-axial joint, and a lateral radiograph showed a 5-mm. gap between the atlas and the odontoid peg. Treatment was by rigid collar splint.

The remaining four patients had subluxation at lower levels of the neck.

A 74-year-old woman with chronic destructive rheumatoid arthritis went to sleep with her head twisted to the right and woke with severe pain localized to the left

occiput. The head was held inclined and rotated to the right; rotation and inclination to the left and extension were painfully limited and accompanied by crepitation. The left sternomastoid muscle seemed to be wasted. Radiographs showed a forward subluxation of C_1 on C_2 and a backward subluxation of C_3 on C_4 with destruction of the $C_3/4$ apophyseal joints but maintenance of the $C_3/4$ disk space.

A 50-year-old woman with severe chronic destructive rheumatoid arthritis with a history of glomerulonephritis and other visceral involvement, taking 30 mg./day prednisolone, developed a pain in the neck spreading to the right shoulder and arm and which did not respond to radiotherapy. Radiograph showed a forward subluxation of C_4 on C_5 with destruction of the $C_4/5$ apophyseal joint. Paraesthesia developed in the lateral halves of both hands, and both triceps jerks were lost. Despite softening of the bone in the articular processes it was possible to protect the unstable region by wiring together the vertebral arches of C_4 and C_5 , following which the patient's pains gradually improved.

A woman with active nodular rheumatoid arthritis of 28 years' duration associated with a negative sheep cell agglutination test, had been treated for 3 years with small doses of prednisolone. The course of her disease was complicated by recurrent phlebitis of the legs, and later by a constant ache spreading to the back of the head and left ear. Neck movements brought on a shooting pain spreading down into the shoulders and both arms and were accompanied by palpable creaking at the C_4 level. X rays showed a forward slip of C_3 on C_4 with narrowing of the $C_3/4$ disk, and also a slight forward movement of C_4 on C_5 . A lateral tomogram showed arthritic destruction of the $C_3/4$ apophyseal joint. There were no neurological abnormalities. Lupus cell preparations did not reveal any true lupus cells, but showed an excess of tart cells and free nuclear material. Treatment by Minerva plaster gave relief of symptoms.

A woman aged 67 with rheumatoid arthritis of 28 years' duration, with grossly swollen and destroyed peripheral joints, regional muscle wasting, a positive sheep cell agglutination test, and an elevated erythrocyte sedimentation rate, developed painful limitation of the neck with marked reduction of lateral flexion and of rotation to the left. X rays showed narrowing of the $C_3/4$, $C_5/6$, $C_6/7$ and C_7/T_1 disks with forward subluxation of C_4 on C_5 and especially of C_7 on C_6 . Prednisone 30 mg./day helped a little, but symptoms were relieved by a plastic Minerva collar.

The authors briefly discuss the problems of treatment. Surgical fixation was worth attempting when the spinal cord was threatened, even though the subjects were usually crippled by severe peripheral arthritis, the bones of the neck were porotic and the surrounding tissues inflamed.

A. St. J. Dixon.

Piston Sign in the Diagnosis of Radicular Compression due to Vertebral Disk Herniation. (El signo del pistón en el diagnóstico de la compresión radicular por hernia discal.) COSTA BERTANI, G. (1960). *Rev. argent. Reum.*, 25, 230.

Gout

Gout and the Serum Uric Acid in Diabetes Mellitus. BECKETT, A. G., and LEWIS, J. G. (1960). *Quart. J. Med.*, 29, 443. 2 figs, bibl.

The serum uric-acid levels in a group of 800 patients with diabetes were lower than the reported figures for non-diabetic subjects. The levels in men were higher than in women. The levels in women increased significantly with age, whereas those for men did not. The lowest values in both sexes were seen in the severe and ketosis-prone types of diabetes, and the highest in patients who were overweight and treated by diet alone. Patients with a family history of gout did not have the higher values normally found in non-diabetic relatives of gouty patients.

A gouty arthritis occurred in eight patients, but was not associated with the high levels of serum uric acid normally seen in gout. In these patients the gout was mild, as was their diabetes, although they did not escape the vascular complications of diabetes.

It is concluded that diabetes increases the excretion of uric acid by a mechanism as yet unknown. Uric acid is considered to have a mild diabetogenic action. A family history of gout is present more frequently in patients with diabetes than in normal subjects. It is possible that a gene linkage exists between the two diseases.—[Authors' summary.]

Urate Diuretic Therapy in Chronic Gout. SMYTH, C. J., FRANK, L. S., and HUFFMAN, E. R. (1960). *Arch. internat. Rheum.*, 3, 3. 4 figs, 38 refs.

The efficacy of oral uricosuric drugs in the treatment of gout is discussed and the results obtained in 66 gouty patients observed over a period of 7 years at three teaching hospitals attached to the University of Colorado School of Medicine, Denver, are reported. It is pointed out that long-term therapy aims at correcting the hyperuricaemia and reducing the excess store of urates in the tissues. Probenecid, in an initial dosage of 1 g. daily, followed by a maintenance dosage arrived at by determination of the serum uric acid level, is recommended for patients who are having more than three or four attacks of gout a year. Long-term therapy with phenylbutazone does not effectively and consistently result in a reduction in the serum urate level, but the drug has been found to be of value in controlling the low-grade aching pain of chronic gout. Salicylates in high dosage are not practical or particularly effective in the long-term treatment of gout and they have the disadvantage of suppressing the uricosuric action of probenecid. Sulphinpyrazone, a phenylbutazone analogue, has been found to be a potent uricosuric agent.

Of the 66 gouty patients 49 received probenecid and seventeen sulphinpyrazone; fifteen of the latter group had previously been maintained on probenecid. The dosage of the drugs varied within the limits of tolerance but aimed at reducing the serum uric acid level to less than 6 mg. per 100 ml. In all cases the severity and frequency of acute attacks were reduced and the existing tophi became smaller. The authors state that a dis-

courageously large percentage of these patients failed to continue long-term treatment. Only 10 per cent. were still being treated at the end of 3 years.

[This is an excellent paper.] *Oswald Savage.*

Prolonged Corticotherapy for Severe Gouty Arthritis.

(Les formes aggravées de la goutte articulaire soumise à la corticothérapie au long cours.) SERRE, H., SIMON, L., and CLAUSTRE J. (1960). *Bull. Soc. méd. Hôp. Paris*, 76, 717. 2 figs, 3 refs.

The authors' experience with prolonged corticosteroid therapy in the management of gout is recorded in this communication from the Clinic of Rheumatology, Montpellier. They show that prolonged administration is never desirable, and that there is rarely any clear indication for steroids to be given, even in short courses. These substances have a limited application as anti-inflammatory agents, but must be given with other more specific drugs. The authors have studied 45 cases of articular gout treated by the prolonged administration of corticosteroids, usually prednisone (deltacortisone). There was an initial amelioration, with relief of pain and inflammation, but the treatment gradually became less and less effective. Any attempt to reduce the dose below a certain minimum was followed by an exacerbation of the arthritis, which was more severe than the original attack and often involved fresh joints. Prolonged steroid administration was found to have no uricosuric action.

It was considered useless to continue with corticosteroid therapy with all its attendant risks and therefore the dosage of prednisone was gradually reduced and the patients treated with colchicine and phenylbutazone. When the steroid preparation had been completely withdrawn, a uricosuric agent was given in addition to colchicine and phenylbutazone. Finally the uricosuric agent was continued alone. It is emphasized that if steroid administration is stopped without these precautions, it may provoke a very severe exacerbation of the gouty arthritis, accompanied by fever and constitutional symptoms.

Kenneth Stone.

Use of the Newer Uricosuric Agents in the Management of Gout.

SEEGMILLER, J. E., and GRAYZEL, A. I. (1960). *J. Amer. med. Ass.*, 173, 1076. 3 figs, 18 refs.

The management of gout following the introduction of the newer uricosuric drugs is discussed in this paper from the National Institutes of Health, Bethesda, Maryland. It is pointed out that colchicine is the drug of choice in acute gouty arthritis, the dosage being 0.5 or 0.6 mg. every hour until symptoms are relieved or toxic effects develop. Gastro-intestinal side-effects are usually avoided if the drug is administered intravenously. Either corticotrophin (ACTH) or phenylbutazone should be given when colchicine therapy fails to bring relief.

Uricosuric drugs are employed if the attacks persist in spite of daily administration of colchicine, or tophaceous deposits are present, or the serum urate level is consistently above 8 mg. per 100 ml. The drugs are given during a quiescent phase in the disease and after colchicine has been taken in maximum tolerated doses, adminis-

tration being continued until the serum uric acid level has become normal. Ancillary measures include a low-purine diet and a fluid intake of more than 3 litres daily. Since alkalinization of the urine increases the solubility of uric acid 4 g. sodium bicarbonate or of trisodium citrate is given three to four times a day. In patients with hypertension or cardiac disease potassium salts may be substituted for the sodium salts.

Of the new uricosuric drugs sulphapyrazone in a dosage of 50 mg. twice daily, increasing gradually to 100 mg. four times daily, is recommended. Alternatively, zoxazolamine may be administered in a dose of about 60 mg. twice a day, increasing over a period of 2 weeks to 125 mg. four times a day. It is pointed out that salicylates antagonize the action of these uricosuric drugs and that uric acid may be precipitated in the urinary tract if adequate precautions are not taken. In cases of tophaceous gout sulphapyrazone or zoxazolamine is indicated if treatment with probenecid causes adverse effects or fails to restore the serum uric acid level to normal.

A. Garland.

Effect of Zoxazolamine on Hyperuricaemia and Uric Acid Excretion in 79 Cases. (Effet de la Zoxazolamine sur l'hyperuricémie et l'excrétion de l'acide urique d'après l'étude de 79 cas.)

MUGLER, A. (1960). *Rev. Rhum.*, 27, 214. 6 figs, 6 refs.

Intravenous Dexamethasone in Acute Gout. (Dexametasona intravenosa en el ataque de gota.)

MORENO, A. RUIZ (1960). *Arch. argent. Reum.*, 23, 67.

Steroid Therapy of Acute Gout. (Tratamiento del ataque de gota por los esteroides.)

MORENO, A. RUIZ (1960). *Arch. argent. Reum.*, 23, 66.

On the Dual Aetiology of Hyperuricaemia in Primary Gout.

WYNGAARDEN, J. B. (1960). *Arthr. and Rheum.*, 3, 414. 2 figs, 15 refs.

Gout Simulating Cardiac Pain.

FRANK, M., DE VRIES, A., ATSMON, A. (1960). *Amer. J. Cardiol.*, 6, 929. 13 refs.

Pararheumatic (Collagen) Diseases

"Delayed" Cutaneous Hypersensitivity to Leukocytes in Disseminated Lupus Erythematosus.

FRIEDMAN, E. A., BARDAWIL, W. A., MERRILL, J. P., and HANAU, C. (1960). *New Engl. J. Med.*, 262, 486. 4 figs, 18 refs.

The incidence of delayed cutaneous reactions to intradermal injection of leukocytes in disseminated lupus erythematosus (D.L.E.) was studied in a number of patients at four hospitals in Greater Boston, Massachusetts. Suspensions of leukocytes from patients and donors were prepared by centrifuging plasma after sedimenting out the erythrocytes of freshly-drawn blood in heparin and dextran at 4° C. for up to one hour. The leukocytes were resuspended in plasma to a concentration of 30,000 to 90,000 per c.mm. and a dose of 0.1 ml. was injected intradermally. Control injections containing

dextran in plasma, dextran solution, or erythrocytes gave negative reactions.

Positive skin reactions to both autologous and donor leucocytes were obtained in sixteen out of twenty patients with D.L.E., two out of seven with typical rheumatoid arthritis (both of whom gave a positive response for the antinuclear factor by the fluorescent antibody technique), and in only one, with osteo-arthritis, out of 51 controls with various diseases. Of the four non-reactors with D.L.E. three were taking at least 20 mg. prednisolone daily. Positive reactions were of the delayed type, maximal at 24 hours, indicating either reactions with fixed cellular antibody or, more simply, the time taken for the inoculated leucocytes to break down and release intranuclear materials able to react as antigens with circulating antibodies. Microscopically the positive reaction differed from the negative reaction in showing accumulations of host cells, mainly polymorphonuclear leucocytes, in the deep dermis and subjacent fat and changes in the overlying epidermal cells. The authors caution against interpreting this reaction as explaining the pathogenesis of D.L.E. or its associated leucopenia.

Allan St. J. Dixon.

Nucleoprotein Complement-fixation Test in the Diagnosis of Systemic Lupus Erythematosus. SCALETTAR, R., MARCUS, D. M., SIMONTON, L. A., and MUSCHEL, L. H. (1960). *New Engl. J. Med.*, 263, 226. 26 refs.

The authors have used a complement-fixation test with crude calf-thymus nucleoprotein as antigen to detect one of the anti-nuclear factors commonly present in the serum of patients with systemic lupus erythematosus (S.L.E.). The test was performed on the sera of 600 healthy and diseased subjects at the Walter Reed General Hospital, Washington, D.C., and showed a positive result in 25 cases. Out of ten definite cases of S.L.E., nine gave a positive titre; the tenth case was also the only one in the group giving a negative L.E.-cell test result. There were ten cases of suspected S.L.E. (only one of which showed a positive L.E.-cell reaction), while six patients with various other diseases gave positive complement-fixation reactions, usually at low serum titres. Successful treatment of S.L.E. with corticosteroids was associated with a fall in the positive titre.

M. Wilkinson.

Diagnosis of Polymyositis. HEATHFIELD, K. W. G., and WILLIAMS, J. R. B. (1960). *Lancet*, 1, 1157. 4 figs, 22 refs.

The authors present from St. Bartholomew's Hospital, London, and Lister Hospital, Hitchin, Herts, a study of 28 cases of polymyositis. In this disorder diagnosis may be difficult, since muscle biopsy may give only normal results, the electrical findings may be misleading, and the clinical picture atypical; fortunately, however, two of these three features are usually positive. The rapid onset of muscular weakness, the occurrence of spontaneous remission, or the elicitation of brisk reflexes at a stage when these would be absent in true muscular dystrophy tend to differentiate the latter condition from myositis. In three of the authors' patients there was

spontaneous fasciculation, with wasting of the tongue. Differentiation from motor-neurone disease is made more difficult by electromyography (EMG), which often shows high-voltage potentials suggesting involvement of anterior-horn cells. One of these patients responded to neostigmine. In considering the collagen diseases it is noted that although skin changes predominate in scleroderma, muscular weakness and wasting are also common. Another possible cause of myopathy is sarcoidosis, and thyrotoxic myopathy must also not be overlooked. In polyarteritis nodosa, the peripheral neuropathy and sensory changes usually underlie the muscular weakness. In five of the present cases there was an association between dermatomyositis (and polymyositis) and carcinoma. Of the 28 cases an abnormal finding on muscle biopsy was obtained in 26.

Typically, there is a myopathic EMG pattern, together with evidence of partial denervation. The latter is shown by the EMG (fibrillation potentials), or by the abnormal, strength-duration curves. Partial denervation, which distinguishes polymyositis sharply from the chronic muscular dystrophies, was present in all but two of the cases. Other pathological investigations are not of great help and in doubtful cases it may be justifiable to use steroids as a therapeutic test. D. Preiskel.

Prognostic Significance of Raynaud's Phenomenon and Other Clinical Characteristics of Systemic Scleroderma. A Study of 271 Cases. FARMER, R. G., GIFFORD, R. W., JR., and HINES, E. A., JR. (1960). *Circulation*, 21, 1088. 39 refs.

Over the 8-year period 1945-52, 488 patients attending the Mayo Clinic were diagnosed as suffering from scleroderma. The case records of these patients have been reviewed by the authors, and 271 patients thought to be suffering from generalized scleroderma (acrosclerosis or generalized progressive scleroderma) have been followed up. The average age at the time of diagnosis was 42.9 years. The onset of the complaint occurred a little earlier in female patients, who accounted for 73.4 per cent. of the series.

At sometime or other during the course of their illness 220 patients experienced Raynaud's phenomenon, this being the initial symptom in 88 of them. In 132 patients the first symptom was stiffness or swelling of the hands and in five trophic changes of the finger tips. Thus no less than 83 per cent. of the patients had their first symptom referable to the hands, whereas involvement of the trunk occurred initially in only 2.6 per cent.

Pigmentation, consisting of a brown discoloration, particularly marked in the areas of sclerosis, was noted in 45 per cent. of the patients. In several patients who were also hypotensive, the extent of the pigmentation led to a diagnosis of Addison's disease being seriously considered. Only 10 per cent. of the patients had calcinosis cutis. No major amputations were necessary, but gangrene of one or more fingers occurred in four patients. Of the 211 patients who were examined radiologically by a barium meal, oesophageal involvement was found in 136 (64.5 per cent.). Despite this finding dysphagia was the presenting symptom in only two patients.

Pulmonary involvement, which was detected by routine chest radiography, occurred in 21 per cent. of the patients and usually consisted of linear fibrosis at both bases. Cardiac involvement was diagnosed in 27 patients (8.9 per cent.) and renal involvement in four, in whom there was evidence of albuminuria and a raised blood urea level. Barium x-ray examinations of the intestinal tract beyond the oesophagus were carried out only when symptoms suggested the necessity. The colon was not found to be involved and clinical evidence of steatorrhoea never detected. Most of the patients in the series had a low-normal blood pressure level, although hypertension (over 160/100 mm. Hg) was present in ten cases (3.7 per cent.). Anaemia, with a haemoglobin value less than 11 g. per 100 ml. (women) or 12 g. per 100 ml. (men) was found in thirty (11.1 per cent.) of the patients. The erythrocyte sedimentation rate (Westergren) was raised to more than 50 mm./hr in 68 (30.5 per cent.) of the patients.

Follow-up information for periods of 5 to 13 years from time of diagnosis was obtained for 236 patients (87.1 per cent.); of these, 115 (48.7 per cent.) had died. The average follow-up period for the 121 living patients was 102 months. Improvement was claimed by 42 patients, 43 considered themselves to be worse, and 36 felt about the same. [This subjective information is of less value than the objective detail given in the study.] The average time between diagnosis and death was 41.2 months and the average age at the time of death was 48.3 years. Amplification of the causes of death was obtained in 83 patients, of whom seventeen had been subjected to necropsy. The most frequent terminal illnesses were congestive cardiac failure, pneumonia, and renal failure with hypertension.

The outstanding fact emerging from this detailed study, however, is that no one factor or group of factors is of any prognostic value. The only distinguishing clinical feature between those with a good and those with a bad prognosis was the rate of progress of the disease. Cardiac and renal involvement, anaemia, and a raised erythrocyte sedimentation rate also seemed to be associated with a poor prognosis.

The authors conclude by pointing out that the prognosis in scleroderma seems to be less favourable than hitherto believed; they also emphasize the need for reclassifying systemic scleroderma. In their opinion the subdivision into acrosclerosis and generalized progressive scleroderma is not only artificial, but has no clinical or prognostic value. They suggest a subdivision into acute, subacute, and chronic systemic scleroderma.

J. Warwick Buckler.

Raynaud's Disease, Raynaud's Phenomenon, and Serotonin. HALPERN, A., KUHN, P. H., SHAFTEL, H. E., SAMUELS, S. S., SHAFTEL, N., SELMAN, D., and BIRCH, H. G. (1960). *Angiology*, 11, 151. 9 figs, bibl.

The part played by Serotonin (hydroxytryptamine) in Raynaud's phenomenon is discussed in this paper from the Angiology Research Foundation, New York, with reference to the findings in eleven female patients (24 to 38 years old), five of whom had primary Raynaud's

disease and six of whom had Raynaud's phenomenon secondary to other conditions. An infusion of Serotonin into the brachial artery of healthy subjects and subjects with Raynaud's phenomenon was followed by vasoconstriction of the hand, with digital cyanosis typical of a Raynaud's attack. When this experiment was repeated after intravenous injection of 1-methyl-D-lysergic acid butanolamide, a Serotonin antagonist, it was found that in the healthy subjects there was an immediate lessening of the cyanotic areas with an abrupt rise in digital temperature, whereas the subjects with Raynaud's disease showed only the beginnings of a reversal of temperature which was incomplete after 15 minutes.

The authors conclude that in healthy subjects a Serotonin-blocking agent only partly and slowly neutralizes the effects of Serotonin on the blood vessels and that the role of Serotonin in the pathogenesis and therapy of Raynaud's disease remains a promising subject for further study.

I. McLean Baird.

Raynaud's Phenomenon treated with Sympathectomy: a Follow-up Study of 28 Patients. HALL, K. V., and HILLESTAD, L. K. (1960). *Angiology*, 11, 186. 3 figs, 9 refs.

Upper-limb sympathectomy for Raynaud's phenomenon was carried out in 28 patients at University Hospital, Oslo. The results after a follow-up period of 6 months to 14 years were classified as excellent (permanent and total relief), fair (reduction in disability or modest improvement), or poor (deterioration). Of 33 upper extremities in nineteen patients with primary Raynaud's phenomenon the results were excellent in 61 per cent. fair in 24 per cent., and poor in 15 per cent. However, of twelve upper extremities in nine patients with secondary Raynaud's phenomenon, excellent results were obtained in only one-third.

The authors conclude that patients with secondary Raynaud's phenomenon show a variable response to sympathectomy and that the best results are obtained in young patients with primary Raynaud's disease.

I. McLean Baird.

Treatment of Primary Raynaud's Disease of the Upper Limb. PEACOCK, J. H. (1960). *Lancet*, 2, 65. 1 fig., 29 refs.

The author reports from the University of Bristol his 4 years' experience in the treatment of 33 patients with primary Raynaud's disease. In a pilot trial reserpine in doses of 0.25 mg. for 2 weeks was effective in increasing the digital blood flow in only two out of six patients. In six patients treated with triiodothyronine, 20 µg. four times a day, there was increase in the resting digital temperature and blood flow, and the cyanotic phase was much shorter than previously.

Reserpine, 0.25 mg. twice daily, and triiodothyronine, 20 µg. four times a day, were then given in combination to all 33 patients with good clinical results. In eight patients no further attacks of pallor and cyanosis occurred, in twenty there were diminished frequency and intensity of the attacks, but in five there was no response. In four out of the five patients who did not respond to

treatment, a single intramuscular injection of 250 mg. testosterone propionate or methylandrostenediol in a dosage of 50 mg. daily was found helpful in reducing the attacks of Raynaud's phenomenon. *I. McLean Baird.*

Treatment of Polyarteritis Nodosa with Cortisone: Results after Three Years. REPORT TO THE MEDICAL RESEARCH COUNCIL BY THE COLLAGEN DISEASES AND HYPERSENSITIVITY PANEL (1960). *Brit. med. J.*, 1, 1399. 1 ref.

An earlier report to the Medical Research Council on this subject (*Brit. med. J.*, 1957, 1, 608; *Abstr. Wld Med.*, 1957, 22, 133) presented the results of one year's cortisone therapy in seventeen patients with polyarteritis nodosa. These were compared, retrospectively, with an untreated group which came under medical care before the days of cortisone treatment. These two groups, however, differed in one important respect, namely, a difference in the incidence of hypertension; this was significantly higher in the untreated group and is important in that it adversely affects the prognosis in this disease.

The present report includes four further treated cases, making a total of 21 biopsy-proved cases which have now been observed for a minimum of 3 years from the beginning of cortisone treatment. Of these 21 patients there were thirteen survivors at 3 years, but three of these died, two in the fourth and one in the fifth year. Of the nineteen untreated patients twelve (63 per cent.) died within 9 months of biopsy, whereas eighteen (86 per cent.) of the treated patients were then still alive. It is essential to note, however, that the untreated group initially included eight patients with hypertension all of whom died within the year, whereas at the start of the study there was only one hypertensive patient in the treatment group, although nine others in this group developed hypertension during the course of the trial. At the end of 3 years thirteen (62 per cent.) of the treated group, as compared with seven (37 per cent.) of the untreated, were alive. This apparent advantage disappears, however, when patients with hypertension are excluded.

The report lays stress on the limitations of this trial, which arose from the unjustifiability of having a concurrent untreated control group. At the start of treatment there was speedy and often dramatic improvement in most patients, but later unpleasant and serious complications developed in a few. The trial has not produced evidence that cortisone, in the dosage given to these patients, improved the chances of ultimate recovery, although it may possibly have postponed death.

G. Loewi.

Pseudo-scleroderma Lesions in Rheumatism. (Lésions pseudo-sclérodérmiques dans le rhumatisme.) JALONSKA, S., and BUBNOW, B. (1960). *Ann. Derm. Syph. (Paris)*, 87, 241. 12 figs, 8 refs.

This report from Warsaw Dermatological Clinic describes the clinical features observed in three patients suffering from chronic polyarthritis associated with scleroderma-like lesions. In all three patients the arthritis was the dominant feature and was present before the skin lesions appeared. The scleroderma patches

differed in several respects from true primary progressive scleroderma, the skin being moist and pale like the skin of patients with chronic arthritis, but differing from the skin appearance in a true scleroderma. The sclerotic plaques were not adherent to the underlying structures. The joints involved included the metacarpo-phalangeal joints and radiographs showed changes consistent with a diagnosis of rheumatoid arthritis. Above all, the skin lesions in these three patients were not progressive. It is concluded that in order to give an accurate prognosis, careful distinction must be made between scleroderma lesions appearing in the course of primary, chronic polyarthritis, and true scleroderma. *G. W. Csonka.*

Treatment of Psoriasis with Subdermal Infiltration of Triamcinolone Diacetate Suspension. GERARD, A. G. (1960). *A.M.A. Arch. Derm.*, 81, 535. 5 refs.

The effect of local injection of steroids on the inflammatory process in psoriasis is discussed and the results obtained with injection of triamcinolone on local lesions are reported. Initially 0.75 ml. of a suspension of triamcinolone diacetate containing 25 mg. per ml. was deposited in the upper layer of the loose, subcutaneous subdermal tissue under a psoriatic lesion, with resolution of the lesion in 5 to 7 days. Similar results were obtained but with slower resolution (14 to 21 days) with suspensions of triamcinolone containing 5 mg., 2.5 mg., and 1.25 mg. per ml. In the treatment of large plaques a preliminary injection of procaine was found to reduce local discomfort. A persistent residual erythema, which occurred with the initial suspension, was not visible when the strength was reduced. The local injection had no effect on other areas of psoriasis in the same patient.

The number of cases and lesions treated is not specified, but the good response was uniform, the skin remaining clear in all cases for 6 months. At the end of 11 months' observation lesions had reappeared in 16 per cent. of cases, but they responded to further treatment. Similar results were obtained with local infiltration of hydrocortisone, but the lesions recurred rapidly. With a combination of triamcinolone and hyaluronidase the results were not materially different from those with triamcinolone only.

Benjamin Schwartz.

Corneal Complications of Chloroquine Treatment; Preliminary Report. [In Swedish.] GABINUS, O., KALLDAL, L., AABORG, C. G., and MERNER, J. (1959). *Svenska Läk.-Tidn.*, 56, 1971. 13 refs.

Chloroquine was given to nineteen patients with collagenoses. None of them reported any ocular complaints, but eight showed patches of diffuse opacities in the epithelium or subepithelially, generally in the lower part of the cornea.

G. von Bahr.

Ophthalmoscopic Manifestations of Dermatomyositis. (Manifestations ophtalmoscopiques des dermatomyosites.) THOMAS, C., CORDIER, J., and DUPREZ, A. (1959). *Bul. Soc. franç. Derm. Syph.*, No. 3, p. 349.

The value of routine fundus examination in collagen diseases and the semeiological value of dysoric nodules are emphasized.

S. Vallon.

Collagen Ocular Disease and its Treatment with Prednisolone. (Afecciones oculares del colágeno y su terapéutica con prednisolona.) CASTIGLIONE, J. F. (1959). *Pren. med. argent.*, **46**, 348. 10 refs.

The author describes the treatment of twenty cases of anterior eye infections (conjunctivitis, keratitis, and phlyctenular episcleritis) with prednisolone (total dose: 100-500 mg.) in several patients of different ages and sex. Good results were obtained and a shorter evolution than usual was observed. No secondary complications occurred. *E. Oblati.*

The Eye in Relation to Collagen Diseases. MANSCHOT, W. A. (1960). *Trans. ophthalm. Soc. U.K.*, **80**, 137. 9 figs, 7 refs.

The pathology of the collagen diseases is reviewed and the ocular lesions are discussed. It is concluded that the ocular manifestations of collagen diseases provide little argument in favour of a pathogenetic relationship of these diseases and that the only reason for combining them into one group is the limited non-specific nature of the connective tissue reaction to noxious agents. *J. M. Heaton.*

Sclero-Keratitis in Erythema Nodosum. (Sklerokeratitis bei Erythema nodosum.) PALICH-SZÁNTÓ, O. (1959). *Ber. dtsch. ophthalm. Ges.*, **62**, 315. 1 fig.

A 57-year-old woman, who many years previously had had a kidney removed because of tuberculosis, was admitted to hospital with erythema nodosum of her legs. She very soon developed an acute inflammation of the eyes, the main characteristic of which was a superficial jelly-like infiltration of the whole limbus near the corneal periphery with abundant vascular neof ormation and ecchymoses. The iris, ciliary body, and fundi were not involved. Eye complications in erythema nodosum described in the literature are either of this type or phlyctenular, and may affect the iris or else appear as chorio-retinitis. Together with erythema nodosum which is definitely related to tuberculosis they have become rare in recent times. Cortisone treatment effected a quick improvement. *L. Wittels.*

Kerato-Conjunctivitis Sicca and the Gougerot-Sjögren Syndrome. (Kérato-conjonctivite sèche et syndrome de Gougerot-Sjögren.) VALIÈRE-VIALEIX, V., and ROBIN, A. (1959). *Sem. méd. (Paris)*, **35**, 1186.

Sjögren's Syndrome in Cushing's Disease after Removal of an Adrenal Adenoma. (Sjögren-Syndrom bei Cushingscher Krankheit nach Entfernung eines Nebennierenrinden-Adenoms.) GERARDY, W. (1959). *Z. Rheumaforsch.*, **18**, 407.

Sjögren's Syndrome in a Male Subject. (Sindrome di Sjögren nel sesso maschile.) PAGANI, L. (1959). *Rass. ital. Ottal.*, **28**, 67. 44 refs.

The Sicca Syndrome (Sjögren's Syndrome): a Study of Sixteen Cases. DENKO, C. W., and BERGENSTAL, D. M. (1960). *Arch. intern. Med.*, **105**, 849. 3 figs, 16 refs.

Pararheumatic (Collagen) Diseases. A Pathogenetic Study (Pararheumatische Krankheiten (Sogenannte Kollagenkrankheiten.) ROST, G. A. (1960). *Arch. klin. exp. Derm.*, **210**, 581. 322 refs.

The L.E. Cell in Rheumatoid Arthritis. TOONE, E. C., JR., IRBY, R., and PIERCE, E. L. (1960). *Amer. J. med. Sci.*, **240**, 599. 39 refs.

Vascular Lesions in Dermatomyositis. BOYLAN, R. C., and SOKOLOFF, L. (1960). *Arthr. and Rheum.*, **3**, 379. 3 figs, 23 refs.

Benign Bilateral Hilar Adenopathy with Erythema Nodosum and Arthralgia. (Considerazioni cliniche ed etiopatogenetiche su un caso di adenopatia ilare bilaterale di natura benigna associata ad eritema nodoso ed artroalgia.) MARRAZZI, G. (1960). *Reumatismo*, **12**, 169. 3 figs, bibl.

Bilateral Hilar Adenopathy with Erythema Nodosum (Löfgren's syndrome). (Adenopatie ilari bilaterali con eritema nodoso.) COSSALI, C., BIELLA, A., and MANIER, L. (1960). *Reumatismo*, **12**, 81. 9 figs, bibl.

Sydenham's Chorea without Evidence of Rheumatic Fever. Report of its Association with the Henoch-Schönlein Syndrome, and with Systemic Lupus Erythematosus. PARADISE, J. L. (1960). *New Engl. J. Med.*, **263**, 625. 46 refs.

(Non-Articular Rheumatism)

Clinical and Experimental Investigation of Fibrositis. (Klinische und experimentelle Untersuchungen zum Fibrositisyndrom.) MIEHLKE, K., SCHULZE, G., and EGER, W. (1960). *Z. Rheumaforsch.*, **19**, 310. 8 figs, 24 refs.

Pain due to Fibrositis in the Soft Tissues of the Upper Body and Treatment with Local Anaesthesia. HEIKINHEIMO, R. (1960). *Arch. interamer. Rheum.*, **3**, 399. 15 refs.

General Pathology

Circulating Antibody Production in Rheumatoid Arthritis. GREENWOOD, R., and BARR, M. (1960). *Ann. phys. Med.*, **5**, 258. 2 figs, 13 refs.

An investigation of the antibody response in rheumatoid arthritis to primary immunization with tetanus toxoid is described in this paper from King's College Hospital, London, and the Wellcome Research Laboratories, Beckenham, Kent. A group of 28 adult patients with active rheumatoid arthritis (diagnostic criteria of the American Rheumatism Association), who were receiving salicylates, hydroxychloroquine, and/or phenylbutazone, were given two injections of tetanus toxoid at 6 weeks' interval. Antibody production at the eighth week was compared by means of a mouse-protection test with that of a control group of 25 healthy subjects "matched for age and sex" [presumably three patients

with rheumatoid arthritis had no paired control] and was found to be significantly greater; nevertheless, in some of the rheumatoid patients the antibody response was poor. Since all the patients were receiving anti-rheumatic drugs, the authors studied the effect of these drugs on antibody production in guinea-pigs, relatively large doses being given. Both chloroquine and salicylate significantly reduced antibody production, but phenylbutazone had no such effect. In the patients with rheumatoid arthritis the antibody titre correlated with disease activity (modified Lansbury index) but not with the sensitized sheep-cell agglutination titre.

The authors briefly refer to the negative results obtained by others in studies of the antibody response in rheumatoid arthritis, and note that these were based on the effect of a booster dose of the antigen rather than on primary immunization. They suggest that the increased antibody response in rheumatoid arthritis may account for other serological abnormalities observed, such as increased streptococcal agglutinins. They mention certain further control studies that need to be carried out [and there are others, such as investigating the responses of sick controls and the question of protective factors other than specific antibody in the mouse-protection tests] before the effect they observed can be attributed to the rheumatoid arthritis in the patients in their series.

Allan St. J. Dixon.

Latex-Particle Slide Tests in Rheumatoid Arthritis. Comparative Study. LANE, J. J., JR., and DECKER, J. L. (1960). *J. Amer. med. Ass.*, 173, 982. 17 refs.

In this study reported from University of Washington School of Medicine, Seattle, the results of two rapid latex-particle slide tests used in rheumatoid arthritis, namely, the R.A. test and the eosin slide test, were compared with those of the latex fixation test, in which agglutination at a dilution of 1 : 160 or greater was regarded as positive. The eosin slide test was performed by adding two drops of stock latex suspension to a well-mixed drop containing serum and a 1 per cent. aqueous eosin solution. A positive result for agglutination produced a stippled granular appearance within 3 minutes. The R.A. slide test involved mixing a drop of the reagent with a drop of test serum diluted to 1 : 20 with glycine-saline buffer solution. The conversion of the cloudy suspension to a clear solution containing clumps was taken as a positive finding.

Sera from 309 cases were examined by all three methods and 65 cases of classic rheumatoid arthritis showed positive reactions in 53, 57, and 58 cases respectively in the three tests outlined above. Rheumatoid arthritis with psoriasis was associated with a lack of agglutinating activity. In ten out of 25 cases of gouty arthritis there were positive reactions with the slide tests, but only one was positive with the standard latex fixation test. Of 55 cases selected as likely to enhance false positive reactions and consisting of diffuse neoplasia and hyperglobulinaemic conditions, about one-third gave agglutination. The two slide tests were found to be more sensitive, but less specific, than the standard latex fixation test. All the positive results in the standard latex

fixation tests were associated with positive results in the slide tests. Hyperglobulinaemia appeared to enhance the number of positive findings in the standard latex fixation test, but the increase in false positive reactions with the slide tests cannot be ascribed to non-specific hyperglobulinaemia. It is concluded that the slide tests are satisfactorily practical and provide a quick method for use in the consulting room.

Harry Coke.

E.S.R. in a New Dress. DAWSON, J. B. (1960). *Brit. med. J.*, 1, 1697. 12 figs, 19 refs.

The investigation here reported from the University of Edinburgh was carried out in an attempt to establish the most convenient method of determining the erythrocyte sedimentation rate (E.S.R.), some of the various modifications of the classic Westergren method being suspected of serious anomalies. After a brief historical review the author discusses the theoretical and practical factors concerned in determining the final numerical value of the E.S.R. and gives a precise definition of the aims of his study. The materials and methods employed are then described in detail. Standard Westergren pipettes were employed and these were usually suspended from hooks according to the method of Duxbury, the distal end being blocked by a rubber cap. It was shown that lateral swinging of the suspended pipette did not affect the result.

The results of the various experiments are analysed statistically and expressed graphically. It is concluded that the best method of determining the E.S.R. is to dilute 2 ml. of a sequestrenized blood sample with one-quarter its volume of isotonic (3.8 per cent.) sodium citrate solution and then examine the rate of fall of the erythrocytes in a freely suspended tube. Good correlation was obtained between this method and a standard method in which oxalated blood diluted with 3.8 per cent. sodium citrate was used, and a similarly good correlation was obtained with the classic Westergren method. The use of undiluted blood to which a solid anticoagulant has been added was shown to give unreliable results with the Westergren pipette. The main advantage in using sequestrene is that deterioration, especially of the nuclei and membranes of abnormal blood cells, is less than with other anticoagulants so that other haematological investigations may be carried out on the same blood sample. It was noted that the use of relatively dirty pipettes which had simply been washed in tap water and allowed to dry did not affect the accuracy of the results. On the other hand increased accuracy was obtained when microburettes and accurate pipettes were employed for making the 1 : 4 dilution of blood and anticoagulant.

From a review of the literature, supported by his own experimental results, the author deduces that Westergren's original normal ranges for the E.S.R. (male adults 0 to 5 mm., female adults 0 to 10 mm. in one hour) are too narrow and that 5 mm. should be added to the upper limit in each case. However, in adults over 50 years of age higher values may be normal, while in pregnancy the normal range is up to 45 mm. in one hour. Normal

neonates have a low E.S.R.—about 2 mm. in one hour by the standard method.

A. Brown.

Serum Mucoproteins. Practical Value of Their Determination. (Les mucoprotéines du sérum. Intérêt pratique de leur détermination.) VARAY, A., and MASSON, M. (1960). *Presse méd.*, **68**, 1323. 6 figs, 34 refs.

The value of estimation of the serum mucoprotein level in relation to hepatic and renal disease, infections, and malignancy is discussed in this paper from the Hôpital Beaujon-Clichy, Paris. The diagnostic significance of over 500 estimations, which included studies on 24 patients with cirrhotic and hepatic jaundice, 32 with obstructive jaundice (both intra- and extra-hepatic), 54 with cirrhosis of the liver, 27 with cancer, and 47 with nephritis, is reviewed. It is concluded that the value of the information obtained with this test in certain contingencies justifies consideration of its regular use as a laboratory diagnostic aid.

H. Harris.

First Trials of C-reactive Protein in Ophthalmology. (Premiers essais sur la protéine C réactive en ophtalmologie.) ROUHER, M.-A. CANTAT, and TRONCHE, P. (1959). *Bull. Soc. Ophthal. Fr.*, No. 12, p. 954. 11 refs.

This protein appears in the blood in allergic disease, as has sometimes been found in the tears of vernal conjunctivitis.

J. Rougier.

Agglutination by Rheumatoid Arthritic Sera of Sheep Red Cells Sensitized with Normal Cattle Sera. TILIKAINEN, A., and MÄKELÄ, O. (1960). *Ann. Med. exp. Fenn.*, **38**, 296. 1 fig., 11 refs.

F.II Agglutinating Factors in Sera of Patients with Non-rheumatic Diseases. HOWELL, D. S., MALCOLM, J. M., PIKE, R., and BROOME, B. (1960). *Amer. J. Med.*, **29**, 662. 1 fig., 51 refs.

Agglutination in Rheumatoid Arthritis Serum of Sheep Cells sensitized with Haemolysin and Infectious Mononucleosis Agglutinins. PIKE, R. M., and SCHULZE, M. L. (1960). *J. Immunol.*, **85**, 523. 3 figs, 20 refs.

Application of Serological Reactions for Rheumatism in Hospital Practice. (Zur praktischen Anwendung der serologischen Rheumatismusreaktionen im Krankenhaus.) KOELSCH, F., and KOELSCH, K. A. (1960). *Z. ges. inn. Med.*, **15**, 941. 5 figs, 5 refs.

Precipitation Reaction with Human Gamma Globulin in Rheumatoid Arthritis. (Reazione di precipitazione e di anafilassi passiva cutanea con gammaglobuline umane in sieri di soggetti affetti da artrite reumatoide.) INVERNIZZI, F., LUPORINI, G., and DEL GIACCO, G. S. (1960). *Reumatismo*, **12**, 155. 34 refs.

Serological Changes in Rheumatoid Arthritis. (Alterazioni siero-immunitarie aspecifiche in malati con artrite reumatoide.) RIZZI, D. (1960). *Reumatismo*, **12**, 150. 26 refs.

Reports on the Serology and Vascular Pathology of Rheumatoid Arthritis. (Rapporti tra sierologia e compromissione anatomoclinica (vascolitica) nell'artrite reumatoide.) BONOMO, L., RIZZLI, D., PINTO, L., and SAPONARO, V. (1960). *Reumatismo*, **12**, 138. 9 figs, 18 refs.

Application of Phenylbutazone in Chronic Rheumatism and its Influence on the Serum Albumin Fractions. (Über Anwendung des Phenylbutazon bei chronischen Rheumatismen und dessen Einfluss auf die serum-eiweissfraktionen.) IMRE, I., and CINTAN, M. (1960). *Z. Rheumaforsch.*, **19**, 345. 18 refs.

Action of Certain Phenylbutazone Derivatives. (Azione clinico-metabolica di alcuni derivati del fenilbutazone.) CIRLA, E., and RATTI, G. (1960). *Reumatismo*, **12**, 76. 3 figs, 7 refs.

Effect of an Anabolic Agent (Nilevar) on Nitrogen and Mineral Metabolism in Two Patients with Rheumatoid Disease. HARRIS, J., BLECHMAN, W., YOUNG, N., MALM, O., and VAUGHAN, J. H. (1960). *Arthr. and Rheum.*, **3**, 341. 2 figs, 26 refs.

Changes in the Serum Electrophoretic Findings in the Course of Acute Rheumatism in the Adult. (Modifications de l'électrophorèse au cours du rhumatisme articulaire aigu de l'adulte.) ABLARD, G., LARCAN, A., GAUBERT, ??., and TARTE, P. (1960). *Rev. Rhum.*, **27**, 406. 1 fig., 22 refs.

Immuno-electrophoresis in the Investigation of the Albumin Bodies of the Interstitial Substance. (Immuno-elektrophoretische Untersuchungen über Eiweisskörper der Kittsubstanz.) FRICKE, R. (1960). *Z. Rheumaforsch.*, **19**, 285. 5 figs, 18 refs.

Electrophoresis and Ultracentrifugation of Serum Proteins in Rheumatoid Arthritis. (L'Elettroforesi e l'ultracentrifugazione delle sieroproteine nell'artrite reumatoide e nella sindrome di aggravamento.) CIRLA, E., SALTERI, F., and FASOLI, A. (1960). *Reumatismo*, **12**, 57. 6 figs, 50 refs.

Influence of Thermal Waters on the Concentration of Serum Glyco- and Mucoproteins. COP, D., RUZDIC, I., DÜRRIGL, T., and MAJSEC, M. (1960). *Arch. inter-amer. Rheum.*, **3**, 426. 2 figs, 18 refs.

The Most Neglected Differential Diagnostic Test in Arthritis [Examination of Synovial Fluid]. HOLLANDER, J. L. (1960). *Arthr. and Rheum.*, **3**, 364. 5 refs.

Acute Glomerulonephritis with Anuria as the First Sign of Acute Articular Rheumatism. (Glomerulonephrite aiguë anurique révélatrice d'un rhumatisme articulaire aigu.) DÉROT, M., and ROY, J.-L. (1960). *Bull. Soc. méd. Hôp. Paris*, **76**, 856.

Stabilizers and Inhibitors in the Sensitized Sheep Cell Agglutination Reaction. FRANKLIN, E. C. (1960). *Arthr. and Rheum.*, 3, 314. 4 figs, 32 refs.

Estimation of Aminopolypeptidases in the Synovial Fluid. (Le dosage des aminopolypeptidases dans le liquide synovial.) RAVAU, P. P., RUITON, P., MAITRE-PIERRE, J., LEJEUNE, E., THOMME, H., and PERRIN, S. (1960). *Rev. Rhum.*, 27, 178.

Examination of the Structure and Function of the Connective Tissue. Untersuchungen über die Struktur und Funktion des Bindegewebes.) FICK, K., FRICKE, R., GATTOW, G., HARTMANN, F., and SCHWARZ, W. (1960). *Z. Rheumaforsch.*, 19, 293. 11 figs, 19 refs.

Immunization to Experimental Arthritis in Rats. HERSHBERGER, L. G., HANSEN, L. M., and CALHOUN, D. W. (1960). *Arthr. and Rheum.*, 3, 387. 1 fig., 5 refs.

Attempt to Produce Systemic Lupus Erythematosus and Rheumatoid Arthritis by Crude Desoxyribonucleic Acid and Joint Antigens. DUBOIS, E. L., and KATZ, Y. J. (1960). *Arthr. and Rheum.*, 3, 403. 10 refs.

Some Carbohydrates of Synovial Fluid. SMITH, J. E., CROWLEY, G. T., JR., and GILES, R. B., JR. (1960). *Arthr. and Rheum.*, 3, 409. 1 fig., 11 refs.

ACTH, Cortisone and Other Steroids

Assessment of the Functional Capacity of the Adrenal Cortex. II. Clinical Application of the ACTH Test. BIRKE, G., DICZFALUSY, E., and PLANTIN, L. O. (1960). *J. clin. Endocr.*, 20, 593. 5 figs, 24 refs.

In a previous paper (*J. clin. Endocr.*, 1958, 18, 736) the authors described an improved method of measuring the functional reserve capacity of the adrenal cortex, based upon the estimation of the urinary excretion of 17-hydroxycorticosteroids before and after administration of corticotrophin (ACTH). In the present paper from Karolinska Sjukhuset and King Gustaf V Research Institute, Stockholm, they report the application of this method to the study of 100 cases of established or suspected adrenocortical disease.

Of eight patients with cortical hyperplasia (manifestations of either Cushing's or the adrenogenital syndrome) six gave an exaggerated response to injection of ACTH. In four patients with benign cortical adenomata and one with a cortical carcinoma there was no response or only a weak one. None of the eleven patients with Addison's disease, including three in whom the resting excretion of 17-hydroxycorticosteroids was in the low normal range, showed any response to ACTH stimulation. Similarly, in three patients who had undergone bilateral adrenalectomy there was no increase in hydroxycorticosteroid excretion following ACTH administration, but five patients with primary hypo-

pituitarism and lowered resting hydroxycorticosteroid levels showed a normal or near-normal response.

ACTH stimulation was also tried in 66 patients in whom adrenocortical hypofunction was suspected on the basis of the presence of at least one of the cardinal symptoms of Addison's disease—loss of weight, weakness, hyperpigmentation, hypotension, hypoglycaemia, and disturbed electrolyte and/or water balance. Few of these patients gave a completely negative response. A diminished response was observed in 43, and most (90 per cent.) of these had two or more suggestive symptoms; only 40 per cent. of those with one symptom, usually weakness, showed a low excretion of corticosteroid in response to ACTH.

The authors suggest that if this technique is used and the results are recorded logarithmically, a valuable method of assessing the endocrine capacity of the adrenal cortex is available. The results of this investigation provide support for the existence of the disease entity of impaired adrenocortical reserve.

H.-J. B. Galbraith.

Post-pubertal Adrenal Virilism with Biochemical Disturbance of the Congenital Type of Adrenal Hyperplasia. BROOKS, R. V., MATTINGLY, D., MILLS, I. H., and PRUNTY, F. T. G. (1960). *Brit. med. J.*, 1, 1294. 5 figs, 20 refs.

From St. Thomas's Hospital Medical School, London, the authors report the cases of three young women aged 18 to 20 who were suffering from a manifestation of the adrenogenital syndrome apparently of the type found in congenital adrenal hyperplasia but appearing for the first time after the onset of puberty. All three patients developed hirsutism and two of them acne after the establishment of normal menstruation. All of them had poorly developed secondary sexual characteristics; biochemical investigation showed their urine to contain an excess of pregnanetriol and this excess was increased further by the administration of corticotrophin. In addition, the urine in all three cases showed an excess of 11-oxy-pregnanetriol while metabolites of cortisol were relatively deficient.

In the authors' opinion this type of adrenogenital syndrome is basically a congenital biochemical lesion which is latent until the underlying defect is brought to light by the changing conditions of puberty. It is emphasized that for the present "this group of patients can only be defined in biochemical terms and distinguished from patients with hirsutism of different origin", as previously described (Prunty and others, *Brit. med. J.*, 1958, 2, 1554; *Abstr. Wld Med.*, 1959, 26, 35).

J. Warwick Buckler.

Adrenocortical Steroids in the Management of Selected Patients with Infectious Diseases. SPINK, W. W. (1960). *Ann. intern. Med.*, 53, 1. 22 figs, 19 refs.

During the period 1950-59, 81 selected patients suffering from various infectious diseases were treated at the University of Minnesota Medical Centre, Minneapolis, with ACTH and adrenocortical steroids in addition to

other therapeutic agents. In the group of 38 patients suffering from shock and peripheral cardiovascular failure due to various bacterial infections the mortality was high (60 per cent.), but nevertheless the steroids appeared to have some beneficial effect. These patients received large intravenous doses of hydrocortisone, up to 1 g. being given in the first 24 hours, after which oral corticosteroid preparations were administered. The remaining 43 patients, who suffered from drug reactions and a variety of infective conditions in which harmful inflammatory reactions, possibly representing a type of acquired microbial hypersensitivity, were prominent, received 200 to 400 mg. hydrocortisone intravenously in 24 hours, followed as in the other cases by oral corticosteroid therapy.

The response to this treatment was extremely good and there were no undesirable side-effects, since the treatment was continued for only a few days. It is concluded that the benefits it conferred far outweighed the possible hazards. A number of illustrative case histories are presented.

Winston Turner.

Clinical, Metabolic, and Endocrinologic Effects of Abrupt Cessation of Maintenance Cortisone Acetate Therapy in Rheumatoid Arthritis. CALKINS, E., ENGEL, L. L., MITCHELL, D. M., CARTER, P., and BAUER, W. (1960). *Arthr. and Rheum.*, 3, 204. 5 figs, 20 refs.

There is evidence that the abrupt cessation of corticosteroid therapy in patients with rheumatoid arthritis is followed by deterioration in the clinical condition and the appearance of symptoms resembling those of adrenal insufficiency. The authors of this paper from the Massachusetts General Hospital and Harvard Medical School, Boston, describe the immediate results of suddenly stopping cortisone treatment in three male patients with rheumatoid arthritis, all of whom had been receiving about 100 mg. cortisone daily for at least 2½ years. Metabolic balance studies were carried out for a few days before cessation of treatment and for several days afterwards.

On the first day after cessation of cortisone administration, sodium retention continued; this was followed by sodium loss for a day or two, and then by sodium retention for several days. This accompanied an increase in plasma volume, while loss of sodium in sweat apparently ceased. Nitrogen, calcium, and phosphorus balances tended to change from negative to positive on stopping cortisone. Symptomatically, headache, anorexia, prostration, and muscular aching were attributed to cortisone withdrawal. Spontaneous improvement after 4 days was accompanied by the reappearance of cortisone metabolites in the urine, indicating a return of natural adrenal cortical activity. A relapse in the arthritic condition also began in all three cases within a day of cortisone withdrawal; joint swelling and stiffness increased, the erythrocyte sedimentation rate rose, and one patient became febrile, without clinical improvement at the 4th day. These symptoms are considered to explain the sodium retention and increased plasma volume which have previously been observed in active rheumatoid arthritis.

J. A. Cosh.

Steroid Arthropathy of the Hip. SWEETNAM, D. R., MASON, R. M., and MURRAY, R. O. (1960). *Brit. med. J.*, 1, 1392. 7 figs, 8 refs.

The authors describe four patients who, while under treatment at the London Hospital during which they received relatively high doses of steroids, developed severe damage to their hip joints with rapid destruction of the femoral head. The fact that these changes, once they started were comparatively rapid and painless, led the authors to suppose that it might have been the steroids which were responsible [although they advance no very convincing reason for this belief]. They agree that even in the absence of steroid therapy severe destruction can occur in these joints in arthritic patients, but point out that then the joint changes are more gradual, less extensive, and pain is a prominent feature.

In discussing causation they suggest that the relief given by steroid therapy may encourage patients to subject damaged joints to over-use, and so precipitate a stage of disorganization which would otherwise have been delayed or might even not have occurred. It is urged that patient on high-dosage steroid therapy should be carefully observed for signs of destruction of the hip-joint.

W. S. C. Copeman.

Caution in Cortisone Therapy of the Eyes. (Gare aux cortisones pour nos yeux.) REGNAULT, J. (1959). *Rev. Path. gén.*, 58, 1353. 1 ref.

In some cases, hydrocortisone eyedrops have induced repeated severe reactions which seem to be related to changes in earth magnetism modifications. S. Vallon.

Adrenocortical Steroid Therapy for Rheumatic Diseases. POLLEY, H. F. (1960). *Arch. phys. Med.*, 41, 497. 14 refs.

Long-term Treatment of Rheumatoid Arthritis with Corticotrophin. COPEMAN, W. S. C., SAVAGE, O., and DAVIS, P. S. (1960). *Arch. interamer. Rheum.*, 3, 334. 4 figs, 9 refs.

Results obtained with Dexamethasone in Rheumatoid Arthritis. GAUDIANO, P., HAVRÁNEK, H., and FORTGIUDICE, H. (1960). *Arch. interamer. Rheum.*, 3, 224. 5 figs, 5 refs.

Treatment of Rheumatoid Arthritis with Dexamethasone: 251 Patients treated for Short and Long Periods. COHEN, A., GOLDMAN, J., KANENSON, W. L., TURNER, R., and ROSE, I. (1960). *J. Amer. med. Ass.*, 174, 831. 7 refs.

Preliminary Report on the Therapeutic Study of Eight New Halogenated Corticosteroids: Evaluation of Hormonal Treatment. ROBLES GIL, J., and KATONA, G. (1960). *Arch. interamer. Rheum.*, 3, 450. 7 figs, 6 refs.

Chemically Modified Adrenocortical Steroids: An appraisal of Their Relative Therapeutic Efficiency in Rheumatoid Arthritis. BOLAND, E. W. (1960). *J. Amer. med. Ass.*, **174**, 835. 15 refs.

Effectiveness of Methylprednisolone and Prednisolone Tertiary-Butylacetate Intra-Articularly in Rheumatoid Arthritis. WOODBURY, J. F. L., and BIECHL, A. (1960). *Canad. med. Ass. J.*, **83**, 836. 9 refs.

Nine Years of Experience with Intrasynovial Steroid Therapy. HOLLANDER, J. L., BROWN, E. M., JR., JESSAR, R. A., UDELL, L., BOWIE, M. A., SHANAHAN, J. R., and STEVENSON, C. R. (1960). *Arch. interamer. Rheum.*, **3**, 171. 15 refs.

Local Effect of Prednisolone Tertiary Butyl Furoate in Rheumatic Diseases—Comparative Results. PÉREZ MATA, J. (1960). *Arch. interamer. Rheum.*, **3**, 197. 2 figs, 32 refs.

Anti-Rheumatic Activity of Dexamethasone Phosphate by Intra- and Peri-articular Injection. (Studio dell'azione antireumatica svolta dal fosfato di desametasone (16-alfa-metil-9-alfa fluoro prednisolone) iniettato per via intra e periarticolare.) GARELLI, R. (1960). *Reumatismo*, **12**, 99. 2 refs.

Intradiskal Injection of Hydrocortisone and Prednisolone in the Treatment of Low Back Pain. LEÃO, LUIZ (1960). *Rheumatism*, **16**, 72. 2 figs, 11 refs.

Electrocardiograms in 53 Patients with Rheumatoid Arthritis after Prolonged Cortisone Therapy. (Osservazioni elettrocardiografiche in 53 pazienti affetti da artrite reumatoide e sottoposti a terapia cortisonica protratta.) EINAUDI, G., and DI VITTORIO, S. (1960). *Reumatismo*, **12**, 67. Bibl.

Use of Na²² to Study the Sodium-retaining Properties of Steroid Therapy in Rheumatoid Arthritis. ANSELL, B. M., and BERNSTEIN, R. E. (1960). *J. chron. Dis.*, **12**, 243. 5 figs, 15 refs.

Problem of Osteoporosis and Pathological Fractures during the Prolonged Treatment of Rheumatoid Arthritis with Corticosteroids. (Observations cliniques sur le problème de l'ostéoporose et des fractures pathologiques au cours d'un traitement prolongé aux corticoïdes chez des patients atteints de polyarthrite chronique évolutive.) GASCON, J., and GRIGNON, C. E. (1960). *Canad. med. Ass. J.*, **83**, 376. 2 refs.

Melanocyte Stimulating Hormone and ACTH Activities of Pituitary Tumors in Patients with Cushing's Syndrome. BAHN, R. C., ROSS, G. T., and MACCARTY, C. S. (1960). *Proc. Mayo Clin.*, **35**, 623. 4 figs, 10 refs.

Cushing's Syndrome Secondary to Focal Adrenal Cortical Hyperplasia. Successful Surgical Treatment by Bilateral Total Adrenalectomy. HARTENAUER, G., and GRAYBEAL, C. E. (1959). *Delaware St. med. J.*, **31**, 177. 8 figs.

Perforation of the Cornea following Cortisone Treatment of Diskiform Keratitis. [In German.] KUNTZ, R. (1959). *Wien. klin. Wschr.*, **71**, 712.

Other General Subjects

Aspirin, Gastro-intestinal Bleeding, and Peptic Ulcer. LEVRAT, M., and LAMBERT, R. (1960). *Amer. J. dig. Dis.*, **5**, 623. 22 refs.

Severe gastro-intestinal symptoms following the oral ingestion of aspirin developed in 52 patients under treatment at the Hôpital Edouard-Herriot, Lyons, during 1957 and 1958. The interval between the last dose of aspirin and the occurrence of symptoms was less than 24 hours. Gastro-intestinal haemorrhage occurred in 39 of the patients; in fifteen of these an active ulcer was demonstrated on x-ray examination, but in 21 the radiological findings were negative and the haemorrhage could not be related to a definite lesion; three patients in this group had alcoholic cirrhosis of the liver. In the remaining thirteen patients in the series no haemorrhage occurred, but x-ray examination revealed an active ulcer. Thus, the presence of active peptic ulcer was radiologically proven in 28 cases. Moreover, in eleven patients in whom the radiological findings were negative there was evidence of what the authors term an "ulcerous predisposition"—that is, a previous healed peptic ulcer and/or a direct family history of peptic ulcer. When these were taken into consideration the number of patients with an ulcerous predisposition became 39 or 75 per cent. of the total.

The pathogenesis is discussed. The authors conclude that the mechanism is mainly that of a local irritant action of the drug on the gastric mucosa, and that this action may have "serious effects in persons of a special constitution".

Joseph Parness.

Importance of Aspirin as a Cause of Anaemia and Peptic Ulcer in Rheumatoid Arthritis. BARAGAR, F. D., and DUTHIE, J. J. R. (1960). *Brit. med. J.*, **1**, 1106. 21 refs.

The case records were studied of 244 patients admitted to the Rheumatic Diseases Unit, Northern General Hospital, Edinburgh, with rheumatoid arthritis, most of whom had been taking aspirin continuously or intermittently in varying dosages for a number of years. The haemoglobin level was determined on admission, on discharge and approximately at 2, 4, and 6 years thereafter. A more detailed study was made of those cases in which the haemoglobin level was significantly low. Although the majority of the patients were taking aspirin regularly, the exact dosage was not always known. The authors therefore selected 75 patients who were taking a minimum of 40 gr. (2.6 g.) and usually 60 gr. (3.9 g.) of aspirin a day, and compared their progress with that of 31 patients who did not receive salicylates or only very occasionally.

Over the 6-year period there was a significant increase in the haemoglobin level in the patients receiving salicylates, which was directly comparable with the increase observed in the smaller group not taking aspirin regularly. Although of all patients, thirty (12.3 per cent.) complained of dyspepsia there was clinical or radiological evidence of peptic ulceration in only ten (4 per cent.). At the final assessment the haemoglobin level in 27 (11 per cent.) patients was below 80 per cent. (100 per cent. equal to 14.8 g. per 100 ml.), but only in three of these was there evidence of peptic ulceration. Although in twelve cases other diseases were present which might possibly have had a bearing on the anaemia, it is considered that the cause of the anaemia in the majority was active rheumatoid arthritis. A review of the literature revealed that the incidence of peptic ulceration in this series compared favourably with that in the general population. It is concluded that regular aspirin can be tolerated for long periods by patients with rheumatoid arthritis, without any increase in anaemia, and that the risk of intra-intestinal haemorrhage or peptic ulceration resulting from salicylate therapy has probably been exaggerated.

J. Warwick Buckler.

Persistence of the "Hydrallazine Syndrome": a Follow-up Study of Eleven Cases. HILDRETH, E. A., BIRO, C. E., and MCCREARY, T. A. (1960). *J. Amer. med. Ass.*, **173**, 657. 16 refs.

The administration of hydrallazine may give rise to a syndrome which initially resembles rheumatoid arthritis, there being migrating arthralgia, followed later on by arthritis or systemic lupus erythematosus with fever, serositis, skin eruptions, splenomegaly, and lymphadenopathy, as well as typical blood changes. It has been reported that if hydrallazine therapy is withdrawn the syndrome disappears whether or not steroid therapy is given, but can be reactivated by further administration of hydrallazine. The literature contains only one report of a prolonged follow-up investigation of a case of the hydrallazine syndrome, and in this case the response to the L.E.-cell test was positive and steroid therapy was required for 14 months after hydrallazine therapy was stopped.

In the present paper from the Hospital of the University of Pennsylvania, Philadelphia, eleven previously unreported cases of the syndrome are described. All the patients were seen at the time of their first reaction and were followed up for 3 to 7 years with careful clinical and serological examinations. Of the eleven patients, nine were females, and while the ages ranged from 24 to 68 years, eight were over 40 years. The average duration of treatment was 23 months (only one patient had received the drug for less than a year) and the average daily oral dose of hydrallazine at the onset of symptoms was 450 mg. In eight patients the appearance of symptoms was closely related in time to a favourable therapeutic response in the blood pressure. The symptoms included joint pains in all eleven patients, joint swelling in five, chest pain and fever in five, and skin rash in three. In four patients all symptoms had disappeared 48 hours after hydrallazine was discontinued and in

three within 28 days. There was evidence of persistent activity in four patients 3 to 7 years after hydrallazine was withdrawn, this consisting in active rheumatoid-like arthritis in two and persistent hepatosplenomegaly in two. Except in these four cases laboratory findings which were originally abnormal tended to return to normal as symptoms cleared. The authors point out that chest pain as a symptom of the hydrallazine syndrome has not previously been reported.

B. M. Ansell.

Fat Metabolism in Rheumatism. [In Russian.] SALAMATINA, V. V. (1960). *Klin. Med. (Mosk.)*, **38**, 100. 1 fig., 9 refs.

The relatively little known subject of fat metabolism in rheumatism has been studied by the author by means of paper electrophoresis in 36 cases of various rheumatic disorders (mainly cardiac) and five cases of collagen disease. In these cases the lipidogram showed a shift to the right, with reduction of the serum α -lipoprotein level and emergence of an O-sub-fraction. The α -fraction was reduced in proportion to the severity of the disease, falling to 10 to 3 per cent. or even to *nil* in patients with severe endocarditis and circulatory failure. Clinical improvement was associated with a rise in the α -fraction to 20 or 25 per cent. The O-sub-fraction was increased in three of nine patients with rheumatic valvular heart disease without manifest endocarditis, and it is suggested that such a rise can serve as an index of patent myocarditis; clinical improvement was associated with a fall in this sub-fraction.

The serum cholesterol level, which is low at the peak of various infectious diseases, was also low (80 to 110 mg. per 100 ml.) in 23 out of the 34 cases of acute endocarditis, myocarditis, and polyarthritis investigated. Furthermore, it was near the lower limits of normal (120 to 130 mg. per 100 ml.) in five such cases and not over 160 mg. per 100 ml. in the remainder; generally the reduction was roughly proportional to the severity of the disease. The serum cholesterol level fell still further (to 70 or 80 mg. per 100 ml.) during the first few days of treatment with ACTH, but in association with subsequent clinical improvement it rose, in many cases, to a hypercholesterolaemic level (220 to 240 mg. per 100 ml.). This course of events was more evident in rheumatoid arthritis than in the other conditions studied.

All these changes seem to be associated with immunological and endocrine reactions, and it is possible that cholesterol is utilized for the production of steroids. Consequently it is suggested that the diet for patients with rheumatic diseases should be revised with these characteristic features of fat metabolism in mind, and that a high-cholesterol diet is indicated.

S. W. Waydenfeld.

Rheumatic Syndromes associated with Pulmonary Neoplasms. (Sull'associazione tra sindromi reumatoidi e neoplasie polmonari.) ZAFFAGNINI, E., and SCHIAVI, G. F. (1960). *Radiobiol. Radioter. Fis. med.*, **15**, 37. 32 refs.

Of 119 patients with cancer of the lung treated at the Radiological Institute of the University of Bologna

during the period 1945-58, 25 (21 per cent.) had rheumatic symptoms. Two syndromes are described, the first of which, the "painful shoulder", occurred in fourteen cases. In twelve of these the rheumatic symptoms preceded those of the lung disease by 3 to 5 months. The pain was usually continuous, but of variable intensity, and might radiate to the elbow, hand, or neck. (No patients with secondary deposits in the supraclavicular or axillary nodes or with tumours of the superior pulmonary sulcus (Pancoast tumours) were included in the series.) Clinical and radiological examination showed no abnormality, but there was a relative eosinophilia in all cases. In eleven cases the primary tumour was in the upper lobe and in three it was in the upper and middle lobes. Improvement followed x-ray therapy in eleven cases and surgery (thoracotomy or pneumonectomy) in two, but this proved only temporary.

The second syndrome (eleven cases) was of a migratory type, affecting various muscles and joints simultaneously or successively. Pain was most commonly felt in the elbow, wrist, and ankle, and was of lesser intensity than in the first type. Again eosinophilia was the only definite abnormality found. In two cases the rheumatic symptoms preceded the pulmonary by a year and in six cases by 2 to 5 months. The effects of treatment were not so marked as in the first type, seven patients improving, but four remaining unchanged. A previous history of rheumatism was not elicited in any of the cases in either group.

The authors point out that rheumatic symptoms may be associated with other pulmonary diseases, such as tuberculosis, chronic empyema, cysts, bronchiectasis, and pleural growths. They attribute them to a non-specific reaction of mesenchymal (collagenous) tissue to various pathogenic agents. The relief following radiotherapy or surgery is ascribed to stress acting through the adrenal-hypophysial system, and the later recurrence of symptoms to exhaustion of the same system by stimuli from the growth. The eosinophilia is taken to be an index of hyperergic mesenchymal reaction, pointing to some form of active participation in the neoplastic process.

The finding of other workers that rheumatic symptoms are almost exclusively associated with squamous-celled types of carcinoma is confirmed, and the possible diagnostic value of these syndromes is pointed out.

J. Walter.

Physical Factors Concerned with the Stiffness of Normal and Diseased Joints. WRIGHT, V., and JOHNS, R. J. (1960). *Bull. Johns Hopk. Hosp.*, 106, 215. 23 figs, 5 refs.

A study of the physical factors concerned with stiffness of normal and diseased joints is reported from the Johns Hopkins University School of Medicine and Hospital, Baltimore. The various components of joint stiffness (elasticity, viscosity, inertia, plasticity, and friction) were measured quantitatively, a device in which a heavy pendulum rotated a shaft and lever which was firmly

attached to the index finger being used; the axis of rotation was carefully adjusted to coincide with that of the second metacarpophalangeal joint. With the pendulum at rest the finger was at the mid-point of normal joint motion, and the maximum amplitude was 30 degrees each side of this joint. Gauges attached to the shaft measured torque, amplitude, and rotational velocity, the results being displayed on a dual-beam cathode-ray tube so that torque was shown against amplitude and velocity.

In a study of 97 non-arthritic subjects it was found that the main components of joint stiffness were the elastic and plastic components and that viscous stiffness was about one-tenth and inertial stiffness about one-hundredth that of elastic stiffness. Frictional stiffness could not be demonstrated. It was also found that elastic stiffness was three to four times greater in the oldest subject (66 years) than in the youngest (4 years). It was increased by cooling the joint and decreased (by about 20 per cent.) by heating to 44° C. Venous occlusion caused a gradual increase in stiffness to a maximum after 30 minutes, but there was a return to normal immediately occlusion ceased. Arterial occlusion resulted in a marked increase in stiffness after 25 minutes, but again this disappeared rapidly when occlusion ceased. No muscular activity could be detected electromyographically during these experiments.

Patients with rheumatoid arthritis showed increased elastic stiffness; in one patient, treatment with steroids reduced the stiffness almost to normal levels. Viscous stiffness was rather greater than in healthy subjects, but was still relatively an unimportant factor. Frictional stiffness was detected in a case of rheumatoid arthritis with gross joint changes and in a case of gout, but it was small in relation to the elastic stiffness present. A patient with systemic sclerosis had increased elastic stiffness while two with Ehlers-Danlos syndrome and seven with Marfan's syndrome had decreased elastic stiffness.

B. E. W. Mace.

Rheumatoid Arthritis, Spondylarthritis Ankylopoietica and Focal Infections in Acute Anterior Uveitis. Incidence, Effect on the Sedimentation Rate, and Duration of Treatment. OKSALA, A. (1960). *Acta ophthal. (Kbh.)*, 38, 322. 37 refs.

Out of 386 patients with acute anterior uveitis (40 per cent. female and 60 per cent. male), 14 per cent. had rheumatoid arthritis, 15 per cent. spondylarthritis ankylopoietica, 36 per cent. osteitis periapicalis, 9 per cent. tonsillitis chronica, 7 per cent. sinusitis maxillaris, and occasionally other possible foci. In 31 per cent. no foci were revealed. The erythrocyte sedimentation rate was higher than normal in about half of the uveitis cases and in those with rheumatoid arthritis or spondylarthritis it was significantly higher than in the other groups. The group with rheumatoid arthritis required longer treatment. Foci did not seem to be of important aetiological significance.

G. von Bahr.

Comparison of Psychological Characteristics and Physiological Reactivity in Ulcer and Rheumatoid Arthritis Groups. I. Psychological Measures. CLEVELAND, S. E., and FISHER, S. (1960). *Psychosom. Med.*, 22, 283. 6 refs.

The authors have already described a set pattern of behavioural activity in patients with rheumatoid arthritis (*Psychosom. Med.*, 1954, 16, 327). At the Veterans Administration Hospital, Houston, Texas, this work on the psychological characteristics of such patients has been repeated and extended. It had previously been found that patients with rheumatoid arthritis have fantasies of a well-defined body-image boundary, reflected in a high "barrier score" on psychological testing, and that by contrast, patients with peptic ulcer have low scores on the barrier scale but have a high "penetration score", reflecting a weak and poorly-defined body-image boundary.

In the present investigation 26 male patients with rheumatoid arthritis and 33 similar patients with peptic ulcer were subjected to a standard interview and the Holtzman ink-blot test (Form B), the interview being directed towards certain limited areas of personality function, for example, participation in athletic and domestic activities and mode of arousal of aggressive feelings. The Holtzman ink-blot test was chosen as being more appropriate than the Rorschach test for such an investigation. In general the results of the previous study were confirmed. Patients with rheumatoid arthritis showed a significantly high degree of participation in sports activities before the onset of the illness. The findings indicated that arthritic patients are intolerant of exhibitionistic behaviour in others because of their own inner aggressive, exhibitionistic impulses. The results of the ink-blot test confirmed that patients with rheumatoid arthritis have a concept of their body image in terms of a well-marked boundary, whereas patients with peptic ulcer regard the body image as being characterized by a vulnerable interior. In each group a pronounced hostile affect was noted; in the rheumatoid group this affect was expressed in terms of athleticism before the onset of the illness, whereas in the ulcer group hostility was experienced as a near-paranoid sense of deprivation by the environment.

A. Balfour Sclaire.

II. Differences in Physiological Reactivity. FISHER, S., and CLEVELAND, S. E. (1960). *Psychosom. Med.*, 22, 290. 3 refs.

In this further study the authors examined the hypothesis that subjects with well-defined body-image boundaries are inclined to channel autonomic excitation via the external body layers and that those with indefinite boundaries display an opposite physiological pattern. Rheumatoid arthritis was chosen as a disease affecting the outer body layers and peptic ulcer as an example of an internal psychosomatic disorder.

In 26 male patients with rheumatoid arthritis and 34 similar patients with peptic ulcer external reactivity was measured by means of the galvanic skin reflex (G.S.R.), and internal reactivity by the heart rate recorded on an electrocardiograph. Simultaneous polygraphic record-

ings of G.S.R. and heart rate were made under two different sets of conditions:

- (1) during an 80-second period of "stress" immediately after the crash of a heavy iron bar falling to the floor;
- (2) during a subsequent 80-second period of relaxation.

The results indicated that under stressful conditions the rheumatoid patients manifested greater G.S.R. than heart-rate activity, while in the ulcer patients the reaction was the opposite, the original hypothesis being thus confirmed. It was noted that during the period of relaxation there was no significant physiological difference between the two groups. This supplementary physiological test would seem to show that when psychosomatic symptoms are induced by stress the patient's previously established tendencies to channel external versus internal responses are likely to be a determinant of the choice of type and site of symptoms.

A. Balfour Sclaire.

Epidemic Cervical Myalgia. DAVIES, D. M. (1960). *Lancet*, 1, 1275. 8 refs.

In the autumn of 1958 and again in the late summer of 1959 a small epidemic of acute myalgia affecting the trapezius muscles occurred among nurses at the London Hospital, thirteen nurses reporting sick out of a total staff of about 725; probably many others were affected to a milder degree and did not seek medical advice. All except one of the thirteen nurses were admitted as patients. The chief symptom was acute pain and tenderness of the trapezius muscles, although this did not necessarily occur at the start of the illness; ten of the patients also complained of mild transient aches in various other muscles and in joints. In some cases there was slight fever for a day or two. The illness, which lasted for an average of 9 days, was not accompanied by any inflammation of the throat or by enlarged glands. The leucocyte count was normal in most cases and the results of the Paul-Bunnell test were negative. The erythrocyte sedimentation rate was raised in only two of the ten cases in which this was estimated. A virus infection was suspected as the cause of this illness, but attempts to identify various viruses by examination of stools or by agglutination or complement-fixation reactions failed.

The author considers that the clinical picture was distinct from that of Bornholm disease and the results of the virological investigations did not support a diagnosis of the latter. Epidemics of acute cervical pain of a very similar character have been described previously.

B. E. W. Mace.

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